EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SMITH KLINE & FRENCH LABORATORIES LIMITED and SMITHKLINE BEECHAM CORPORATION d/b/a GLAXOSMITHKLINE,	)	
Plaintiffs,	)	Civil Action No. 05-197-GMS
v.	)	
TEVA PHARMACEUTICALS USA, INC.,	)	
Defendant.	)	

PLAINTIFFS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

Plaintiffs Smith Kline & French Laboratories Limited, and SmithKline Beecham Corporation d/b/a GlaxoSmithKline (collectively "GSK") set forth below its proposed findings of fact and conclusions of law and reserves the right to supplement this exhibit and/or the proofs offered at trial.

I. Proposed Findings of Fact

A. Introduction

1. This is a patent infringement action in which the plaintiffs (collectively, "GSK") contend that Teva infringes claim 5 of U.S. Patent No. 4,452,808 ("the '808 patent") and claim 3 of U.S. Patent No. 4,824,860 ("the '860 patent").

2. GSK is a pharmaceutical company headquartered in the United Kingdom with operations based in the United States. It is a recognized industry leader with an estimated seven percent of the world's pharmaceutical market. It sells over 100 major branded pharmaceutical products throughout the world. PTX 311.

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3. GSK scientists invented, and GSK developed, makes and sells REQUIP®, which is used to treat patients suffering from Parkinson's Disease and Restless Legs Syndrome. PTX 353; PTX 419; PTX 423.

4. Teva Pharmaceutical Industries Limited is a global pharmaceutical company that markets and sells generic drugs. Manufacturers of generic drugs seek to sell cheaper versions of branded drugs by avoiding the substantial costs associated with the research and development of a newer, safer and more effective therapeutics.

5. Claim 5 of the '808 patent is a claim to a chemical composition that covers ropinirole hydrochloride, the chemical name for REQUIP. PTX 13. Claim 3 of the '860 patent is a method claim directed to the use of ropinirole hydrochloride to treat Parkinson's disease. PTX 35.

6. In December 2004, Teva filed an Abbreviated New Drug Application ("ANDA") to obtain approval from the United States Food and Drug Administration ("FDA") to engage in the commercial manufacture and sale of ropinirole hydrochloride tablets, prior to the expiration of GSK's patents. PTX 65; Ex. 1 to the Proposed Pretrial Order, ¶ 12.

7. Teva stipulates that its ANDA submission constituted an act of infringement under 35 U.S.C. §271(e)(2) of the asserted claims to the extent those claims are valid and enforceable. Ex. 1 to the Proposed Pretrial Order, ¶ 16.

8. Teva's primary defense is that the asserted claims would have been obvious. Teva also asserts that the claims are unenforceable because of alleged acts of inequitable conduct committed with respect to both patents by the named inventors.

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B. Background

1. The Effect of Parkinson's disease on the Central Nervous System and Its Treatments

a) The Unique Properties of Nerve Cells

9. Parkinson's disease is a debilitating and slowly progressive disorder of the *central nervous system*[1] ("CNS"). PTX 300, PTX 302, PTX 382. The central nervous system consists of the brain and spinal cord. Nerves are the bundles of fibers that convey impulses such as sensation and motion between the brain or spinal cord and other parts of the body.

10. Nerve cells are different from all other cells in the body. They can conduct electrical signals for long distances without any loss of signal strength. Nerve cells make specific connections with each other, as well as with the tissues that they innervate such as muscles and blood vessels. These connections convey information to the target cell or tissue and can in turn receive a response.

11. The point of connection between two nerve cells or between a nerve cell and a tissue is called a *synapse*. An individual nerve cell may divide at its tip into thousands of branches, each of which can form a synapse with a different nerve cell or the tissue it innervates. That same individual nerve cell can itself receive thousands of inputs by forming synapses with other nerve cells. The diversity of connections between nerve cells, and the amount of information capable of being processed, is enormous.

[1] Italicized terms are defined in the glossary included as attachment A.

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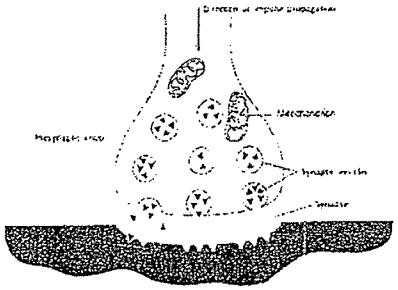
From Snyder, S. H., *Drugs and the Brain,* 1996 at page 5.

12. The billions of interconnected nerve cells in the human body do not come into actual physical contact with one another. Each synapse consists of the terminal of one nerve cell (*presynaptic terminal*) and the beginning of another nerve cell (*postsynaptic end*), and a gap between the two ends, called the *synaptic cleft*. When an electric signal generated by a nerve cell reaches the presynaptic tip of that cell at the synapse, it causes the release of a burst of a special chemical substance into the synaptic cleft. This chemical substance (of which there are many different types) is called a *neurotransmitter*, and it diffuses rapidly across the synaptic cleft and binds to a specific *receptor* in the membrane of the target nerve cell at its postsynaptic end. The interaction of the neurotransmitter with the receptor acts to either speed up or slow down the rate at which the target nerve cell generates its own electrical signals. It can shorten or lengthen the intervals between the target cell's pattern of electrical firing, depending on whether it is an

excitatory or an inhibitory neurotransmitter.



From Snyder, S. H., *Drugs and the Brain*; 1996, at page 8.

13. Just as a lock recognizes a key, the specific receptors to which neurotransmitters bind are proteins imbedded in the membrane of the target cell that specifically recognize that neurotransmitter. A neurotransmitter cannot alter the activity of a cell that lacks its specific receptor, and so only certain nerve cells will be affected by a specific neurotransmitter.

14. The process of the neurotransmitter passing across the synaptic cleft and binding to its receptor is known as *synaptic transmission* and, in time scale, it is rapid and brief. As soon as the neurotransmitter has interacted with its receptor and initiated an electrical signal in the target cell, it is removed both from the receptor and from the synaptic cleft, thus making the receptor available for the next burst of neurotransmitter to be released. The removal of the neurotransmitter is most often achieved by pumping it back into the nerve cell from which it was originally released by a process known as reuptake. Some neurotransmitters, however, are destroyed in the synaptic cleft by special enzymes or simply float or diffuse away from the area of the synaptic cleft.

b) How Drugs Affect Neurotransmission

15. A chemical compound or drug can influence synaptic transmission in different

ways. All neurotransmitters must be manufactured, or synthesized, from other biochemicals in a series of steps carried out by special enzymes. A drug that inhibited one of these enzymes would also impede the formation of the neurotransmitter. For example, certain chemical compounds used to treat high blood pressure act by blocking the formation of *norepinephrine*. Norepinephrine is a neurotransmitter that, when released from its nerve cells, raises blood pressure among other actions. Other drugs affect the release of the neurotransmitter from the nerve tips, inhibit the enzymes that destroy the neurotransmitter, or block the reuptake inactivation process.

16. The most common approach is to use a drug to influence the receptor to which the neurotransmitter binds. Some drugs may be recognized by a receptor in the same way that it recognizes its natural neurotransmitter, and have the same effect on the target cell as the neurotransmitter itself. These compounds are called *agonists* and they, in effect, mimic the neurotransmitter that exists naturally in the body. Other drugs may be recognized by the receptor but not in a way that has any direct effect on the target cell; rather, they simply block the neurotransmitter from occupying its receptor and, thus, prevent its effect. These compounds are called antagonists.

c) Catecholamines are a Class of Neurotransmitters

17. In mammals, epinephrine, norepinephrine and dopamine are important neurotransmitters. These three compounds are members of a class of neurotransmitters *catecholamines*. The term *catecholamine* refers to all organic compounds that contain a *catechol* nucleus and amine group. *See infra* ¶ 39. Epinephrine, norepinephrine and dopamine are vitally involved in the regulation of a wide variety of organ functions in parts of the body outside of the

brain, such as heart rate and blood pressure. The catecholamine neurotransmitters interact with their specific receptors to produce such effects, but the receptors come in a variety of different forms that control different actions of each neurotransmitter. These are known as receptor sub-types and serve to increase control on the effects of a neurotransmitter in the nervous system. Catecholamines also act in the brain and are found in delineated nerve tracts that innervate discrete brain regions. In essence, these compounds act as chemical messengers responsible for transmitting signals within the brain and throughout the rest of the body.

18. Dopamine was the last catecholamine neurotransmitter to be discovered. In the brain, dopamine is found in highly organized and delineated series of nerve tracts that innervate a range of brain areas. These nerve tracts control the higher functions of the nervous system, such as movement, pleasure, memory and learning, and emotion. One particular dopaminergic tract is found within an area of the brain known as the *basal ganglia*. This area of the brain is intimately involved in allowing body movement. The dopamine producing nerve cells originate in a part of the basal ganglia known as the *substantia nigra*. This name reflects the fact that these cells contain a black pigment termed neuromelanin. The nerve cells send projections to another area of the basal ganglia known as the *striatum*, or as more commonly referred to in man, the *caudate-putamen*. In the striatum, dopamine is released and acts on target cells that possess dopamine receptors. This action initiates a chain of events that leads to signals being generated from the basal ganglia that allow movement throughout the body to occur.

d) Parkinson's disease

19. As many as one million Americans currently suffer from Parkinson's disease and approximately 50,000 Americans are diagnosed with Parkinson's disease each year. PTX 300,

PTX 302. While Parkinson's disease generally affects people over the age of 60, it can also develop in younger people. PTX 300.

20. The characteristic immobility of Parkinson's disease patients is caused by degeneration of dopamine-containing nerves running between the substantia nigra and the striatum, two parts of the brain that control motion in the body. *See infra* ¶ 19. The absence of dopamine causes nerve cells to fire uncontrollably and results in slowness, stiffness and tremor.

21. The symptoms of Parkinson's disease include slowness of movement (called "*bradykinesia*"), stiffness, tremor, stooped posture, imbalance, and shuffling gait. PTX 300, PTX 302. Patients typically live with symptoms of Parkinson's disease for 15 years or more, but experience progressive motor disability. As the disease progresses, the symptoms of Parkinson's disease can begin to interfere with walking, speech, and other daily activities. In the late stages of the disease, this may include the inability to walk independently and difficulty swallowing, leading to fall-related injury, choking, aspiration, pneumonia, and death. The type and severity of symptoms vary by patient and even for a given patient at different stages of the disease.

22. There is no known cure for Parkinson's disease. The treatment of Parkinson's disease patients consists of managing the symptoms primarily through the use of drugs. Over time, the medical treatment of Parkinson's disease becomes less satisfactory. Patients are often troubled by intermittency of response to medications (motor fluctuations), and other motor complications such as involuntary movements (*dyskinesias*). Patients also develop difficulty with speech, freezing of gait, imbalance and falls.

23. To maintain mobility, the dopamine normally released by the brain in a healthy person must be replaced with medication. Thus, the main avenue of treatment for Parkinson's

disease is to replace dopamine, as the cells that produce it are lost as a result of the disorder.

24. It is widely understood that treatment for Parkinson's disease must be individually tailored. The appropriate treatment may vary depending on the patient. Treatment may also vary for a given patient as different symptoms occur throughout different stages of his or her illness. Most Parkinson's disease patients are treated with a combination of drugs that changes over the course of the disease.

25. The mainstay of treatment over the last 40 years has been a compound called levodopa or "L-Dopa." Levodopa is a dopamine precursor that gets absorbed by the brain and *metabolized* into dopamine.

26. In a large number of patients, long-term treatment with levodopa is associated with the development of motor complications, such as dyskinesias and motor fluctuations. Patients with longstanding Parkinson's disease develop intermittency of response and "off" periods when medication effects decrease, sometimes unpredictably. Factors related to the development of motor complications in Parkinson's disease include the dose and duration of levodopa treatment and the progression of the disease. Accordingly, one common treatment strategy is to minimize the cumulative levodopa dosage employed over the course of the disease, particularly early on.

27. *Dopamine agonists* are a separate class of drugs for the treatment of Parkinson's disease. Rather then being actually converted into dopamine itself like levodopa, dopamine agonists mimic dopamine and act directly on dopamine receptors in the brain. Because dopamine agonists have a longer half-life and more specific mechanism of action, they do not lead to early onset of motor fluctuations and dyskinesias.

28. Dopamine agonists can be used effectively as an *adjunctive treatment* along with

levodopa or alone as *monotherapy*. As an adjunctive therapy, dopamine agonists are used in the treatment of patients having difficulties sustaining a stable motor response to levodopa. In this context, a dopamine agonist is added on to levodopa as a second drug.

29. Five dopamine agonists are now FDA approved for the treatment of Parkinson's disease. Bromocriptine and pergolide are older *ergoline-type* dopamine agonists, but are not currently favored as a treatment option due to their association with uncommon but medically serious adverse advents like pulmonary fibrosis (scarring of the lung tissue) and heart valve changes. Apomorphine is a short-acting dopamine agonist and must be taken by injection, which is inconvenient for patients. The two newer non-ergoline dopamine agonists -- REQUIP and pramipexole (Mirapex®, sold by Boehringer Ingelheim) -- do not suffer from the same serious problems as the bromocriptine and pergolide.

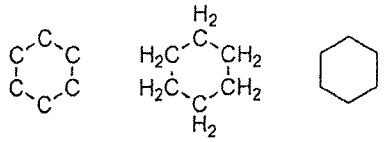
2. *Organic Chemistry* and Dopamine Agonists

a) *The Structures of Organic Compounds*

30. At their most basic level, dopamine agonists are organic *molecules*. Molecules are comprised of groups of atoms bonded together in a particular pattern. Organic molecules are a specific subset (which includes most medicinal agents) and are typically composed of carbon (C), hydrogen (H), nitrogen (N), and oxygen (O) atoms, sometimes with some additional elements. The atoms of each element engage in a characteristic number of bonds when they are joined with other atoms in a molecule. Hydrogen forms only one bond, while oxygen forms two bonds, nitrogen forms three bonds, and finally, carbon forms four bonds.

31. The structures of molecules can be conveyed with words (chemical nomenclature) or pictures (graphical forms). In graphical representations, lines denote bonds that link the atoms

together. Thus, a ring of six carbon atoms could be displayed as shown in A below. This very simple structure does not represent a stable molecule, as each carbon must make 4 bonds; a stable molecule with 6 carbons in a ring could be cyclohexane, shown as B, with two hydrogens bonded to each carbon to satisfy the 4-bond requirement. When the hydrogen atoms are attached to the carbons on the ring the convention is to indicate the number of hydrogen atoms attached by using a subscript numeral. Therefore, in the case of B each carbon is attached to two other carbons and attached to two hydrogen atoms for a total of 4 bonds. To write out all these carbons and hydrogens is cumbersome, so the conventional shorthand is simply to omit them, showing only the bonds that link the carbons together, as in C. A chemist recognizes that each vertex in this hexagon represents a carbon atom, and that each carbon atom has enough hydrogens attached to make the 4 bonds needed for stability.



A B C

Cyclohexane

32. Atoms may be connected together by so-called *single bonds*, represented by single lines, or by *double* or *triple* bonds, represented by double or triple lines, respectively. The double and triple bonds are counted among the four bonds to a carbon atom, hence each double (or triple) bond reduces by one (or two) the number of other connections a carbon atom can make. Thus, a chemist recognizes that two of the carbons in cyclohexene have only one hydrogen atom attached, whereas the others have two:

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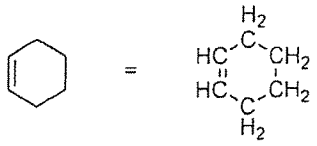
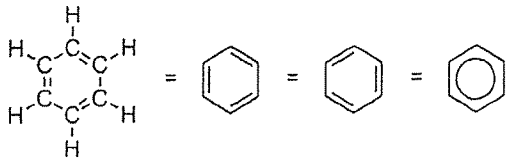


Cyclohexene

33. A special kind of 6-membered ring system arises when three double bonds are contained within the ring, as in the structure of benzene. The double bonds interact with each other and lose their individual identity, so these rings are sometimes depicted simply with a circle inside the hexagon rather than with the individual double bonds. Such molecules are called *aromatic compounds* for historical reasons, although the designation refers to their special chemical behavior (not necessarily to their fragrance).



Equivalent representations of benzene

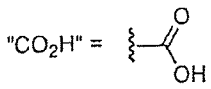
34. In addition to simple rings constructed from carbon and hydrogen, organic molecules may also have chains of atoms (often represented graphically by zigzag lines) and, as indicated above, they often contain additional elements such as nitrogen, oxygen, chlorine, etc. (which are indicated by their atomic symbol at the appropriate position on the structure).

35. Chemists have developed additional terms that refer to different parts of a chemical structure. For example, the molecular *framework*, consisting of the carbon backbone and ring systems that may be present, is often distinguished from the *substituents* that are appended to it. Substituents typically replace a hydrogen atom that would be present at that position in the

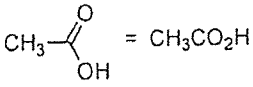
structure, and they may be simple atomic replacements or more complex *functional groups*.

36. Functional groups are common molecular fragments that have characteristic chemical properties. The fragment with the composition "CO_2H", for example, is a carboxylic acid group that may convey acidic properties to molecules in which it is found, as illustrated by acetic acid (vinegar) and benzoic acid (a food preservative):

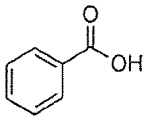
The carboxyl functional group



Acetic acid



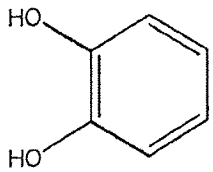
Benzoic acid



37. Other common functional groups include the *hydroxyl group* (–OH), common to alcohols, and the *amino group* ($–NH_2$). Chemists also distinguish between *primary* amino groups, in which the nitrogen atom bears two hydrogens, *secondary* amino groups, in which one of the hydrogens has been replaced with an alkyl group, and *tertiary* amino groups, in which both hydrogen atoms have been replaced.

b) Catecholamines

38. Catecholamines are a category of neurotransmitters. See infra 17. The term catecholamine refers to all organic compounds that contain a catechol nucleus and an amine group. A catechol nucleus is a benzene ring with two adjacent hydroxy groups (referred to as –OH in nomenclature terms):



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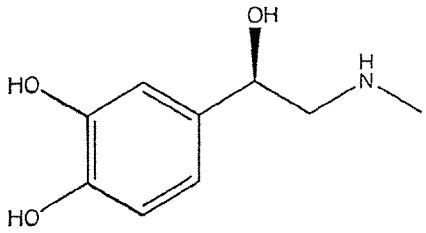
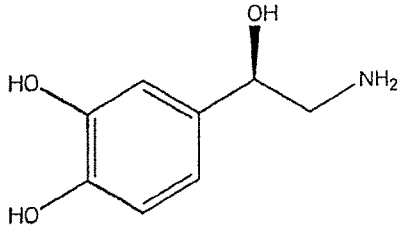
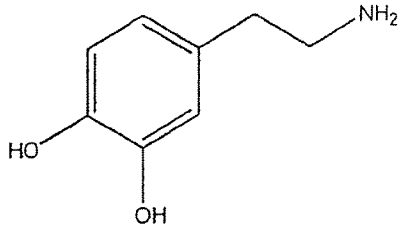
39. The three catecholamine neurotransmitters common to mammals, epinephrine, norepinephrine and dopamine, differ in the types of atoms attached to the amine group or to the carbon atoms between the amine group and the catechol nucleus, but they all share in common the catechol nucleus with its hydroxy groups:



epinephrine



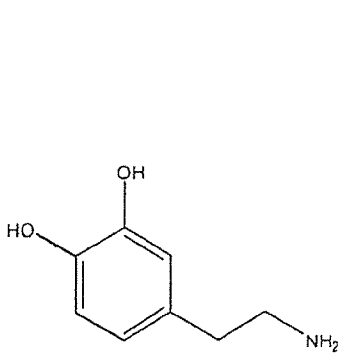
norepinephrine



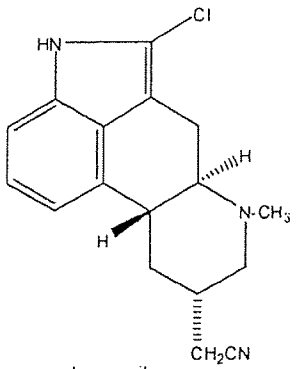
dopamine

40. Ropinirole, which is the common name for REQUIP, is a dopamine agonist and therefore mimics dopamine's action in the body. A number of the concepts outlined above are

illustrated in the structures of the neurotransmitter dopamine and the dopamine agonist lergotrile:



Dopamine

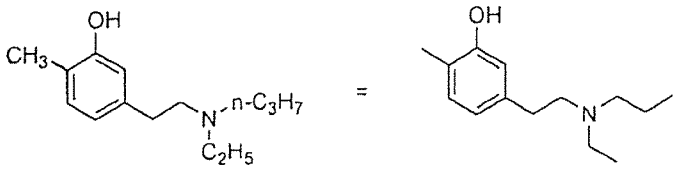


Lergotrile

41. In the structure of dopamine, the two hydroxyl groups (OH) are substituents on the aromatic ring, taking the place of two hydrogens that would otherwise be connected to the carbon atoms at those positions. Lergotrile has a tetracyclic framework (i.e., it has four rings), two of which are called *heterocyclic rings* because they contain non-carbon atoms (in this case, nitrogens). To this framework are appended chlorine (Cl) and methyl (CH_3) substituents, along with a "cyanomethyl" (CH_2CN) functional group.

42. Common substituents are often designated by formula, rather than being drawn out, even if they represent collections of atoms. *Alkyl groups*, for example, which are fragments of simple, singly-bonded hydrocarbons, are often represented in this way. The formulas for methyl (CH_3) and ethyl (C_2H_5) groups are unambiguous, whereas for larger groups such as the 3-carbon propyl group, an additional designator is required to indicate whether it is attached at a carbon at the end of the chain ("n-propyl" or n-C_3H_7) or the middle of the chain ("i-propyl" or i-C_3H_7). The hypothetical structure below illustrates these points, along with a tertiary amino group as

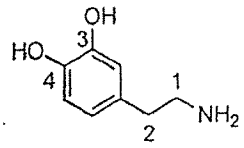
discussed above:



c) **Isomers**

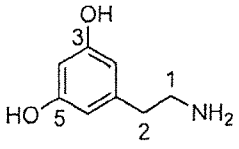
43. The dopamine molecule is composed of 8 carbon atoms, 11 hydrogen atoms, two oxygen atoms, and one nitrogen atom. These atoms can be connected to each other in different patterns, to give molecules with different structures other than dopamine. Molecules with the same composition but different structures are called *isomers*. Two of the many isomers of dopamine are depicted below by way of illustration.

Dopamine

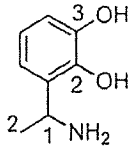


2-(3,4-dihydroxyphenyl)-ethylamine

Two out of many possible *isomers* of dopamine



2-(3,5-dihydroxyphenyl)-ethylamine

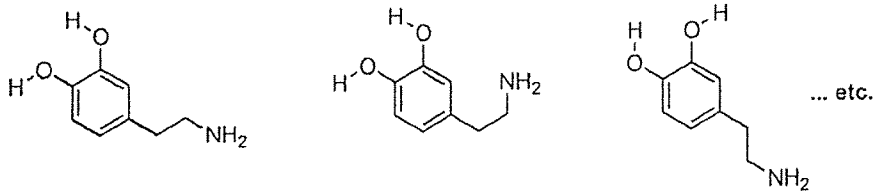


1-(2,3-dihydroxyphenyl)-ethylamine

For complex structures, hundreds, and in some cases thousands, of isomers are possible. Because molecules like dopamine exert their biological activity by interacting with other molecules, their structure - how the atoms are connected to each other in 3-dimensions - is of paramount importance. Thus, isomers may have vastly different activities, despite having the same composition.

44. Organic molecules are 3-dimensional in nature, hence simple 2-dimensional

drawings such as those above may not convey all their structural complexities. In addition, molecular structures are dynamic because single bonds allow the parts of the molecules that they connect to rotate relative to each other. These different 3-dimensional forms are referred to as *conformations* of the molecule. Thus, the dopamine molecule continuously interconverts between conformations such as those depicted below, as well as conformations in which the aminoethyl ($CH_2CH_2NH_2$) side chain lies out of the plane of the ring. The conformations that a molecule is able to adopt depend on its structure, hence medicinal chemists often attempt to limit the flexibility of a molecule and constrain it to the "bioactive" conformation by introducing rigidifying rings into the framework. Indeed, many of the dopaminergic compounds discussed below arose from such attempts.



Different conformations of the dopamine molecule

d) The Nomenclature of Organic Compounds

45. Organic chemists have developed both systematic and common nomenclatures for complex organic molecules. Thus, as illustrated above, "dopamine" can be designated as 2-(3,4-dihydroxyphenyl)ethylamine, a name that not only specifies every component of the structure, but also the manner in which they are attached to each other.

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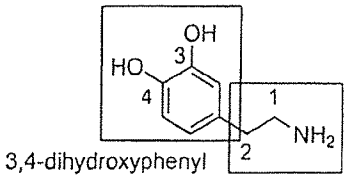
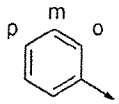
Formal nomenclature for dopamine



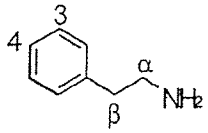
The *3,4-dihydroxyphenyl* group is attached to the 2-carbon of *ethylamine*



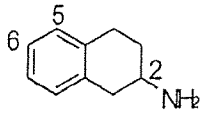
Positions on phenyl substituents may also be designated as *ortho*, *meta*, or *para* relative to the point of attachment

46. A key element of systematic nomenclature is the numbering scheme, which enables structural isomers to be distinguished. For example, the molecules corresponding to 2-(3,5-dihydroxyphenyl)ethylamine and 1-(2,3-dihydroxyphenyl)ethylamine are isomers of dopamine.

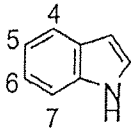
47. Not surprisingly, the formal names of complex molecules are too cumbersome to use routinely, so common names are employed instead. Some of the ring systems relevant to the present litigation are illustrated below with their common names.



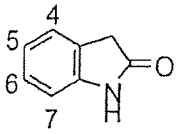
β-Phenethylamine



2-Aminotetralin



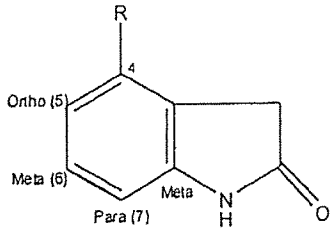
Indole



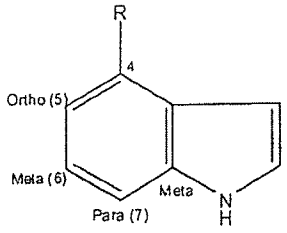
2-Indolone

48. As shown above, chemists employ a numerical scheme to identify different positions on the ring structure of a compound. Functional groups (*i.e.* the amino group) are usually number one in a given numerical scheme. Then, in the case of ring systems as well as other structures, the numbers increase as you migrate around the ring skipping those carbon positions that are involved in fusion of the two ring systems. Chemists often talk about substitution on the benzene ring as being "ortho," "meta," or "para." See Infra. ¶22. In the case of substituted *indoles* and *indolones* the substitution can occur at many points on the benzene ring, but in this

case the indole and indolone compounds are all substituted at the 4 position. Therefore, with a group substituted at the 4 position any further substitution at position 5 would be ortho to that group; substitutions at position 6 and 8 are meta to that group; and substitutions at position 7 are para to that group; which is illustrated below:



Indolone



Indole

C. The Patents-In-Suit

1. The '808 Patent

a) Drug Discovery In General

49. The discovery of a new drug is a difficult process that involves the intersection of many scientific disciplines. Enormous experimental effort is undertaken to identify biologically active *lead compounds* and optimize them for evaluation as drug candidates. Lengthy and expensive testing is required to determine if these candidates are suitable for administration to man. Finally, extensive *clinical trials* are carried out to determine if they are efficacious and safe.

50. The discovery of a new pharmaceutical agent begins with the consideration of a disease area, such as cancer, heart disease, diabetes, or neurological disorders. In some cases, a researcher may be able to focus his or her attention on a specific biological mechanism of action,

often referred to as a *target* that is known to play a role in the disease. In particularly favorable circumstances, it may be possible to probe the function of the biological target in a simple *in vitro* system (i.e., in a test tube – or the modern equivalent), which facilitates the evaluation of drug candidates that may show promise in treating the disease.

51. However, in other cases, a specific biological target for treating the disease may not have been identified, in which case a researcher must rely on animal testing (an "*in vivo*" model) to evaluate the promise of potential lead compounds phenomenologically. The researcher may thus be able to identify the biological target only after compounds effective in modulating the disease have been found and their mechanism of action elucidated.

52. Even in instances in which a target may have been identified biologically, the complexity of the system in which it functions may be such that the effect of increasing or decreasing its activity cannot be evaluated in a simple *in vitro* experiment. Indeed, the complexity of every biological system is such that any drug must be evaluated in extensive animal and, eventually, clinical trials before its efficacy and potential toxicity can be fully understood.

53. From the standpoint of a medicinal chemist, the starting point in the search for a new drug is a "lead compound;" a molecule that shows some of the desired biological activity. There are a number of ways in which such starting points can be identified. One approach is to build on what is known in the art by considering what compounds have been described in the scientific literature or in patents as showing the desired activity.

54. It is essentially never the case that a medicinal chemist is able to identify a lead compound, either from screening or from the prior art, which has all the properties required of a

new drug. Invariably, modifications to the structure are undertaken to change the properties so that it has the desired potency and selectivity for the biological target, an acceptably low toxicity when tested in animals, it can be adequately absorbed from its site of administration (optimally by oral dosage), and to ensure that it is distributed throughout the body and not metabolized or excreted too slowly or too quickly.

b) The '944 Patent

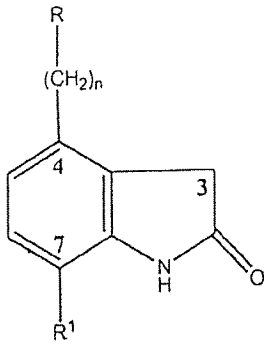
55. In the case of ropinirole, the lead compound was first described in a prior GSK patent, U.S. Patent No. 4,314,944 ("the '944 patent"), naming Dr. William Huffman and Dr. James Wilson as inventors. PXT 36.

56. In the late 1970s and early 1980s, Dr. Huffman worked as part of the chemistry group within the anti-anginal/anti-hypertensive program at GSK looking new drugs with beneficial cardiovascular activity.

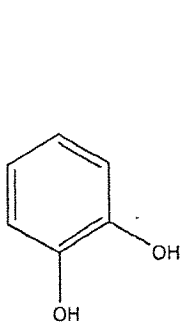
57. As part of this program, Dr. Huffman synthesized some indolone compounds in the hope that they would mimic dopamine. The structure of the dopamine receptor was not known. As a result, researchers such as Dr. Huffman naturally looked to the structure of dopamine itself in the search for drugs that would successfully interact with the dopamine receptor. The hypothesis underlying Dr. Huffman's work at the time was that in order to mimic dopamine, the indolone compounds would need either a catechol nucleus or a *catechol mimetic*.

58. Dr. Huffman's work led to the compound known as SKF 89124. SKF 89124 was the basis for the '944 patent which discloses a new group of 2(3H)-indolones whose structures are characterized by a 2(3H)-indolone (oxindole) nucleus having an aminoalkyl substituent at the 4-position and an oxygen function at the 7-position. PTX 36. The generic formula claimed in the

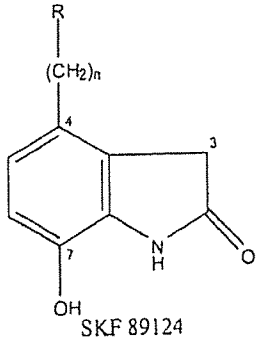
'944 patent is shown below:



SKF 89124 is an indolone and a catechol mimetic, meaning that it has a structure that resembles a catechol. PTX 36. SKF 89124 is considered a catechol mimetic because the R^1 substituent (which can be a hydroxy (-OH) or a methoxy (-CH_3OH) group) and the nitrogen of the pyyrole ring to the right of the benzene ring mimic the hydroxyl groups that are present on a true catecholamine, as shown below.



Catechol



SKF 89124
(where R_1 is a hydroxy)

59. The compounds of the '944 patent are described as having beneficial cardiovascular effects and supporting pharmacological data are disclosed for a number of the claimed compounds. PTX 36. The '944 patent also contains six examples. Examples 1, 2, 5, and 6 teach

methods of preparing 7-methoxylated 2(3H)-indolones having varying substituents at the 4-position while examples 3 through 6 teach methods of preparing 7-hydroxylated 2(3H)-indolones having varying substituents at the 4-position. Example 1 is a working example while example 6 is a prophetic example. Examples 2 through 5 are combinations of working examples and prophetic examples.

60. The application leading to the '944 patent was filed on August 20, 1980. The '944 patent issued on February 9, 1982. PTX 36.

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c) **The Discovery of Ropinirole**

62. Gregory Gallagher, now retired, was a medicinal chemist also employed at GSK. At the time of his invention in 1982, Mr. Gallagher was working in the anti-anginal/anti-hypertensive program looking for new drugs with beneficial cardiovascular activity.

63. In that context, Mr. Gallagher was assigned to work with the Huffman compound, SKF 89124 as a lead compound.

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EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

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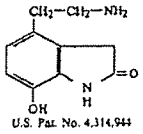
d) The '808 Patent Specification And Claims

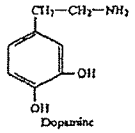
66. The application for the '808 patent was filed on December 7, 1982. PTX 13, Ex. 1 to the Proposed Pretrial Order, ¶ 17. Mr. Gallagher is the sole inventor. *Id.*

67. The patent disclosed in its specification the closest prior art – the indolones identified in the '944 patent – and explained why Mr. Gallagher's invention was not obvious in light of that art.

The basic structure of the prior art compounds is similar to that of the well known cardinvascular agent they mimic, dopamine:



U.S. Pat. No. 4,314,944



Dopamine

One skilled in the structure function art will appreciate that the 7-hydroxy group of the compounds of the prior art is necessary for them to resemble the structure of dopamine. Without this key group, the resulting compounds would not be expected to have cardiovascular activity.

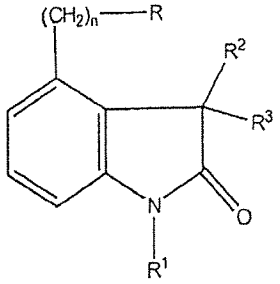
68. The '808 patent describes two different methods, labeled as Scheme A and Scheme B, by which to synthesize the 4-aminoalkyl-2(3H)-indolone compounds disclosed in the '808 patent.

EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

69. The compounds of the '808 patent are disclosed as being peripheral dopamine agonists (*i.e.*, dopamine agonists that work in the peripheral nervous system, rather than the central nervous system) with beneficial cardiovascular activity as evidenced by supporting pharmacological data for ropinirole hydrochloride. The '808 patent contains nine examples. Example 1 teaches how to make ropinirole hydrochloride by applying Scheme A while example 2 teaches how to make ropinirole hydrochloride by applying Scheme B. Examples 3 through 8 teach methods of preparing compounds of the patent with various 4-position substituents. Example 8 also teaches methods of preparing compounds with 3-position substituents. Example 9 teaches how to make a ropinirole formulation for administration to patient. Examples 1 and 2 are working examples, while examples 3 through 7 and 9 are prophetic examples. Example 8 is a combination of a working example and a prophetic example.

70. Claim 1 of the '808 patent is recited below:

A compound of the structural formula:

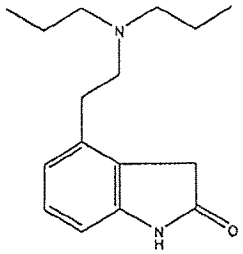


in which: n is 1-3, R is amino, C_{1-6}-lower alkylamino, di-(C_{1-6}-lower alkyl)amino, allylamino, diallylamino, N-(C_{1-6}-lower alkyl)-N-allylamino, benzylamino, dibenzylamino, phenethylamino, diphenethylamino, 4-hydroxyphenethyl amino or di-(4-

hydroxyphenethyl)amino, and R^1, R^2 and R^3 are, each, hydrogen or C_{1-4}-lower alkyl; or a pharmaceutically acceptable, acid addition salt thereof.

71. Claim 4 is directed to ropinirole: "The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone as the free base."

72. The structural formula of ropinirole is as follows:



Ropinirole

73. Claim 5 – the claim at issue – claims ropinirole hydrochloride itself; that is, ropinirole that has become a salt through the addition of hydrochloric acid: "The compound of claim 1 being 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride."

74. Mr. Gallagher's claims were allowed by the Patent Office in a First Office Action. PTX 13. The '808 patent issued on June 5, 1984. Ex. 1 to the Proposed Pretrial Order, ¶ 17.

2. The '860 Patent.

a) The Invention Leading To The '860 Patent

75. In the fall of 1985, further development of SK&F 101468, as ropinirole was then called, was transferred from GSK's operations in the United States to its facilities in Welwyn, England ("Welwyn").

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EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

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77. In 1985, Dr. David Owen was the head of the Pharmacology Department at Welwyn and the senior pharmacologist responsible for cardiovascular programs in the UK. He did not become directly involved in the development of ropinirole until after the transfer. Once Welwyn assumed responsibility of SK&F 101468, Dr. Owen determined that *conscious animal studies* (*acute and repeat dosing studies*) were necessary to further understand the cardiovascular effects of ropinirole.

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EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

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EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

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b) The '860 Patent Disclosure And Claims

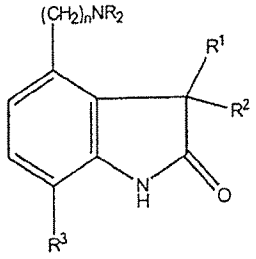
85. The U.S. application for the '860 patent was filed on May 19, 1988. PTX 35, Ex. 1 to the Proposed Pretrial Order, ¶ 19. A U.K. patent application, upon which the U.S. '860 patent application claims priority, was previously filed on May 21, 1987. *Id.* Dr. Owen is the sole inventor. *Id.* The indolone derivatives disclosed in the '860 patent include some of the compounds disclosed in the '944 and '808 patents. The '860 patent discloses the discovery that these prior art indolone compounds, previously thought to be peripheral dopamine agonists, exhibit central nervous system effects and could be used for the treatment for Parkinson's disease.

86. There are seven examples (A-G) in the '860 patent. Example A describes the effect of ropinirole hydrochloride, one of the claimed compounds, on spontaneous *locomotor* activity in mice. The results of this test indicate that ropinirole hydrochloride has dopamine agonist activity. Example B describes the ability of ropinirole hydrochloride to induce stereotypy in rats or mice. The results of this test are indicative of a more selective mode of dopamine agonist action. Example C demonstrates that ropinirole hydrochloride has anti-Parkinson potential based

on its effect on locomotor activity in the rat. Example D shows that ropinirole hydrochloride exhibits statistically significant anti-depressant activity based on its effect in the *Porsolt Test.* Example E demonstrates ropinirole hydrochloride's anxiolytic effects and example F demonstrates the anti-Parkinson activity of ropinirole hydrochloride in the *MPTP-Treated Marmoset Model.* Example G shows the results of receptor binding studies, demonstrating that ropinirole hydrochloride is more selective in its binding to dopamine receptors than other D_2 agonists, bromocriptine and pergolide. All of the examples in the '860 patent are working examples.

87. Claim 1 of the '860 patent is recited below:

> A method of treatment of Parkinson's disease which comprises administering an effective non-toxic amount for the treatment of Parkinson's disease of a compound of the following structure:



> in which each group R is hydrogen or C1-4 alkyl; R1 and R2 are each hydrogen or C1-4 alkyl; R3 is hydrogen or hydroxy; and n is 1 to 3; or a pharmaceutically acceptable salt thereof to a subject in need thereof.

88. Claim 3 is directed to a method of treatment of Parkinson's disease with ropinirole: "A method of treatment of Parkinson's disease which comprises administering an effective non-toxic amount for the treatment of Parkinson's disease of 4-(2-di-n-propylaminoethyl)-2-(3H)-

indolone hydrochloride to a subject in need thereof."

D. Ownership of the '808 and '860 Patents

89. The '808 patent is assigned on its face to SmithKlineBeckman Corporation. PTX 68, Ex. 1 to the Proposed Pretrial Order, ¶ 18. In 1989, SmithKline Beckman changed its name to SmithKline Beecham Corporation. Ex. 1 to the Proposed Pretrial Order, ¶ 4. In 2000, after GlaxoSmithKline plc acquired its corporate parent SmithKline Beecham plc, SmithKline Beecham Corporation began doing business as GlaxoSmithKline. Ex. 1 to the Proposed Pretrial Order, ¶ 4. Accordingly, SmithKlineBeecham Corporation d/b/a GSK is the owner of the '808 patent.

90. The '860 patent is assigned on its face to Smith Kline & French Laboratories Limited. PTX 69, Ex. 1 to the Proposed Pretrial Order, ¶ 21. In 2000, after GlaxoSmithKline plc acquired its corporate parent SmithKline Beecham plc, Smith Kline & French Laboratories Limited began doing business as GlaxoSmithKline. Ex. 1 to the Proposed Pretrial Order, ¶ 2. Smith Kline & French Laboratories Limited d/b/a GSK is the owner of the '808 patent.

E. Infringement

91. Teva filed an Abbreviated New Drug Application seeking the approval of its ropinirole hydrochloride tablets in December 2004 (ANDA No. 77-460). PTX 65, Ex. 1 to the Proposed Pretrial Order, ¶ 12.

92. Teva admits that the drug product for which ANDA No. 77-460 seeks FDA approval contains as the active ingredient ropinirole hydrochloride, and that its tablets are bioequivalent to GSK's ropinirole hydrochloride tablets. Ex. 1 to the Proposed Pretrial Order, ¶ 12.

93. Teva submitted its ANDA No. 77-460 to obtain FDA approval to engage in the

commercial manufacturer, use and sale of ropinirole hydrochloride tablets, prior to the expiration of GSK's patents.

94. Teva's submission of ANDA No. 77-460 and its amendments constituted an act of infringement of claim 5 of the '808 patent claim 3 of the '860 patent. Ex. 1 to the Proposed Pretrial Order, ¶ 16.

95. Teva's making, using, selling, offering to sell, or importing ropinirole hydrochloride tablets that Teva seeks approval to market under the Teva ANDA would infringe claim 5 of the '808 patent, and Teva's making, using, selling, offering to sell, or importing ropinirole hydrochloride tablets for use in the treatment of Parkinson's disease would indirectly infringe claim 3 of the '860 patent, except to the extent that such making, using, selling, offering to sell, or importing of the products was performed solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use or sale of drugs or veterinary biological products, including the submission of the Teva ANDA.

F. Validity

1. Non-Obviousness of The '808 Patent

96. Teva's sole claim of invalidity with respect to the '808 patent is that the compound of claim 5, ropinirole hydrochloride, would have been obvious to one of ordinary skill in the art at the time of the invention.

97. In support of its obviousness contention, Teva cites various scientific publications, which it claims would have made it obvious to modify a chemical, compound existing in the prior art to make ropinirole hydrochloride.

EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

a) The Level Of Skill In the Art

98. In the chemical arts, obviousness requires one of ordinary skill in the art to have a reasonable expectation of success. "[O]bvious to try" is an incorrect standard. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). The presence of a reasonable expectation of success is measured from the perspective of a person of ordinary skill in the art at the time the invention was made. *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000).

99. Gregory Gallagher did not have any advanced degree in chemistry. At the time of his invention, he had been working as a medicinal chemist at GSK for approximately 15 years. Prior to his invention, Mr. Gallagher had never worked with dopamine agonists.

100. GSK's employees working in the field of *medicinal chemistry* did not specialize in particular classes of compounds, and there were no such employees specializing in dopamine agonists.

101. Medicinal chemistry in general is not segmented by classes of compounds. Most medicinal chemists work on a variety of classes of compounds during their career.

102. The primary pieces of prior art relied on by Teva appear in general journals of medicinal chemistry rather than specialized journals relating to dopamine agonists.

103. A person of ordinary skill in the art at the time of the invention would have been an individual with an advanced degree (M.S. or Ph.D.) in organic chemistry or pharmacology and having two or three years of laboratory experience in medicinal chemistry in an academic or industry setting. A person without a graduate degree, but having more laboratory experience in this field, could also be considered a person of ordinary skill at the time of the invention.

104. Teva's technical experts are Drs. Joseph Cannon and John Paul Long and they are

also authors of some of the prior art on which Teva relies. GSK's technical experts are Dr. Paul Bartlett (primarily with respect to the '808 patent) and Dr. Peter Jenner (primarily with respect to the '860 patent). Drs. Cannon and Long have specialized in the study of dopamine agonists for over 40 years. They define the art of the '808 patent as "the design and synthesis of biologically active pharmaceutical compounds that are structurally similar to dopamine." (Cannon Rep. at ¶41.) According to Dr. Cannon, there are "50, maybe a hundred people, 150 people country-wide" who practice in this art, including himself and Dr. Long. (Cannon Dep. 88:5-6, Oct. 19, 2006). Dr. Long in turn assumed that those of ordinary skill in the art would need to be an expert. (Long Dep. 165:16-19, October 17, 2006). The relevant art is far broader than dopimanergic compounds and the level of ordinary skill therefore lower, and more general, than the level posited by Teva's experts.

b) The Content Of The Prior Art

105. Based on *"Structure-Activity Relationships (SAR),"* Teva apparently contends that it would have been both obvious to modify an existing chemical compound to make ropinirole hydrochloride and that a person of ordinary skill in the art would have expected such a compound to be suitable as a pharmaceutical compound. In its expert reports, Teva identifies the following references as purportedly rendering claim 5 of the '808 patent obvious:

a. The '944 patent together with "the state of the knowledge in the prior art."

b. Cannon, J.G., Demopoulos, B.J., Long, J.P., Flynn, J.R. & Sharabi, F.M. Proposed dopaminergic *pharmacophore* of lergotrile, pergolide, and related ergot alkaloid derivatives. *J Med Chem.* 24, 238-240 (1981) ("the Cannon 1981 article") in light of "state of the knowledge in the prior art."

c. The combination of the Cannon 1981 article and the '944 patent.

c) Structure-Activity Relationships (SAR)

106. In the search for novel and improved drugs, scientists may use a conceptual approach known as "structure-activity relationships" or "SAR." In a SAR analysis, a medicinal chemist looks for a trend in a property of interest, for example a biological effect in an *in vitro* or *in vivo* model system, as the structures of the molecules are modified. To the extent a researcher tries to glean from SAR analyses some indication of which compounds to make and which compounds to avoid, hypotheses of this sort may be of potential use in guiding his decision. The utility of such hypotheses are critically dependent on the type of data from which they are derived and on the nature of the extrapolation that the researcher makes in applying them to an unknown structure.

107. For example, a typical SAR hypothesis could be as follows: a researcher observes that the replacement of a particular hydrogen atom with a hydroxyl group (OH) leads to an improvement in activity between one pair of molecules, therefore, he might hope to see a similar difference in activity if the same substitution is made in a closely related pair of molecules. For there to be any validity to this inference, all other elements of the experiment must be the same; *i.e.*, the activity must be measured under similar conditions and against the same target. As one would expect, the more that the comparison compounds differ from each other, the less confidence the researcher can have in his hypothesis.

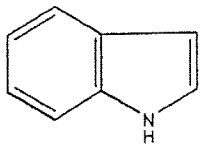
108. A SAR hypothesis derived from one kind of data provides no insight into properties that depend on different types of data. For example, if one simply determines the *in vitro* activity of two related compounds, one containing a hydroxyl substituent and the other a

hydrogen, this information is not useful for inferring what the difference between the compounds would be in terms of their absorption, tissue distribution, metabolism, excretion, toxicity - in short, their efficacy as drugs *in vivo*. This is because data derived from experiments performed outside of a living animal is obviously not the same as data derived from experiments performed on a live animal.

109. One can have little confidence in the generality of a SAR analysis that is based on data derived from an experiment that contains many variables. For instance, if the biological test involves an *in vivo* animal model system that depends on a CNS effect, the molecular interaction between the lead compound and the biological target will be only one factor out of many in determining the observed activity. For one series of compounds, the activity may be affected by the potency of the molecule, whereas for another series penetration of the *blood-brain barrier* may restrict the observed effect. Since these various biological properties are not affected by structural alterations in the same way, the SAR observed for one series of compounds may be completely irrelevant for another.

c) Compound 9

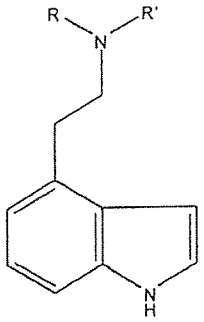
110. The '944 patent is discussed above. See infra ¶¶ 55-61. With respect to the Cannon 1981 article, Teva principally relies on an indole identified as "Compound 9" in the paper. As noted above, an indole has the following structure:



Indole

EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

Compound 9's structure is as follows:

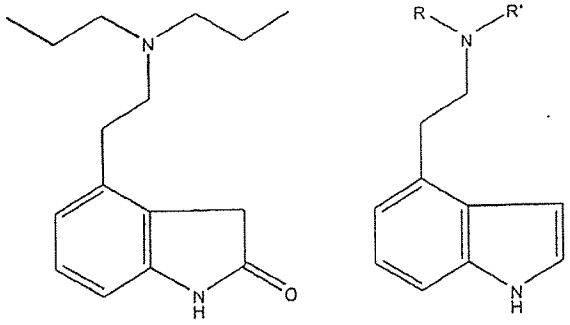


Compound 9
(Indole)

111. Compound 9 differs from ropinirole because it is an indole, while ropinirole is an indolone. The structural difference between the two compounds is at the 2 position of the heterocyclic ring. In ropinirole there is a *ketone group* at the 2 position, but in compound 9 there is a carbon-carbon double bond between the 2 and 3 positions. The consequence of this change is that the heterocyclic ring is no longer aromatic. Changes in aromaticity can often affect how a molecule will interact with a receptor. Further, the presence of the ketone group changes the acidity of the hydrogen attached to the nitrogen. The hydrogen is now more acidic which makes it more available for hydrogen bonding with the receptor. Ultimately, this change also affects the electron distribution within the molecule as well as the overall lipophilicity.

As illustrated in the diagram below, the structural change can appear deceptively simple. It appears that all that was done is a simple substitution at the 2 position of the heterocyclic ring. However, this is a prime example of why two-dimensional chemical drawings provide an incomplete picture. Receptors are three-dimensional in nature and require a certain three-dimensional structure, electronic character, and polarity of the compound before the compound

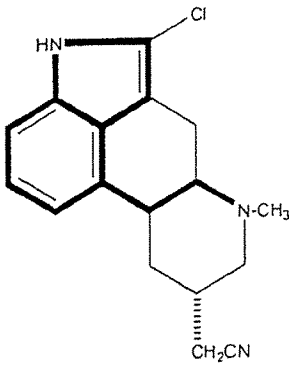
can properly bond with and modulate the activity of the receptor. This drawing does not convey any of the changes in electron distribution that results from the loss of aromaticity in ropinirole, nor does it convey the increased availability of the hydrogen for bonding with the receptor.



Ropinirole (Indolone) Compound 9 (Indole)

112. In the 1981 Cannon Article, Dr. Cannon proposed Compound 9 as the pharmacophore (*i.e.*, the portion of a molecule responsible for its biological activity) to explain dopaminergic activity of dopamine agonists known as ergot alkaloid derivatives. *Ergot alkaloids* are compounds that resemble naturally occurring molecules found in the fungus Claviceps purpura, which infests rye and causes ergotism (characterized by hallucinations, vasoconstriction, and miscarriage). One example of an ergot alkaloid is legotrile, shown below, in which the structure of compound 9 has been highlighted:

EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

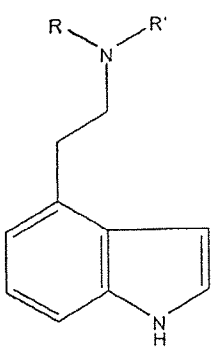


113. Cannon hypothesized that Compound 9 demonstrates dopaminergic activity in the absence of hydroxy groups. However, in the same publication, the authors reported that the activity of Compound 9 in vivo in cats required 30-40 minutes to become maximal following intravenous administration. Cannon recognized, and his paper taught, this fact as showing that Compound 9 was likely to require conversion *in vivo* to account for its activity: "This slow rate of onset of action may indicate *metabolic activation.*" The Cannon 1981 Article at 240.

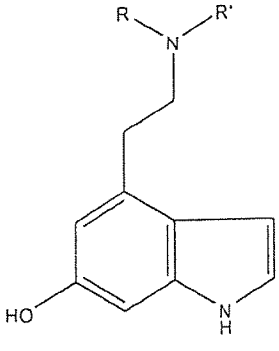
114. Further, in the 1981 Cannon Review Article, Cannon recognized that the "metabolic activation" might be "by *hydroxylation* of the benzene ring" and that Compound 9 "may also represent a *prodrug* to a dopaminergic agonist." A "prodrug" is a compound that itself has little or no biological activity but which becomes biologically active after it is metabolized, either by adding or subtracting functional chemical groups to or from the prodrug.

115. A person skilled in the art would appreciate that the hydroxylation of the benzene ring of Compound 9 could result in a compound having an OH group in the meta position on the ring as shown below:

EXHIBIT 20 TO PROPOSED PRETRIAL ORDER



Compound 9
(Indole)



Compound 9
Active Metabolite

116. In 1984, Cannon himself confirmed his earlier observation that Compound 9's dopaminergic activity was attributable to its 6-hydroxy metabolite. Cannon, J.G., Lee,T., Ilhan, M., Koons, J. & Long, J.P. 6-Hydroxy-4-[2-(di-n-propylamino)ethyl]indole: synthesis and dopaminergic actions. *J. Med. Chem.* 27, 386-389 (1984).

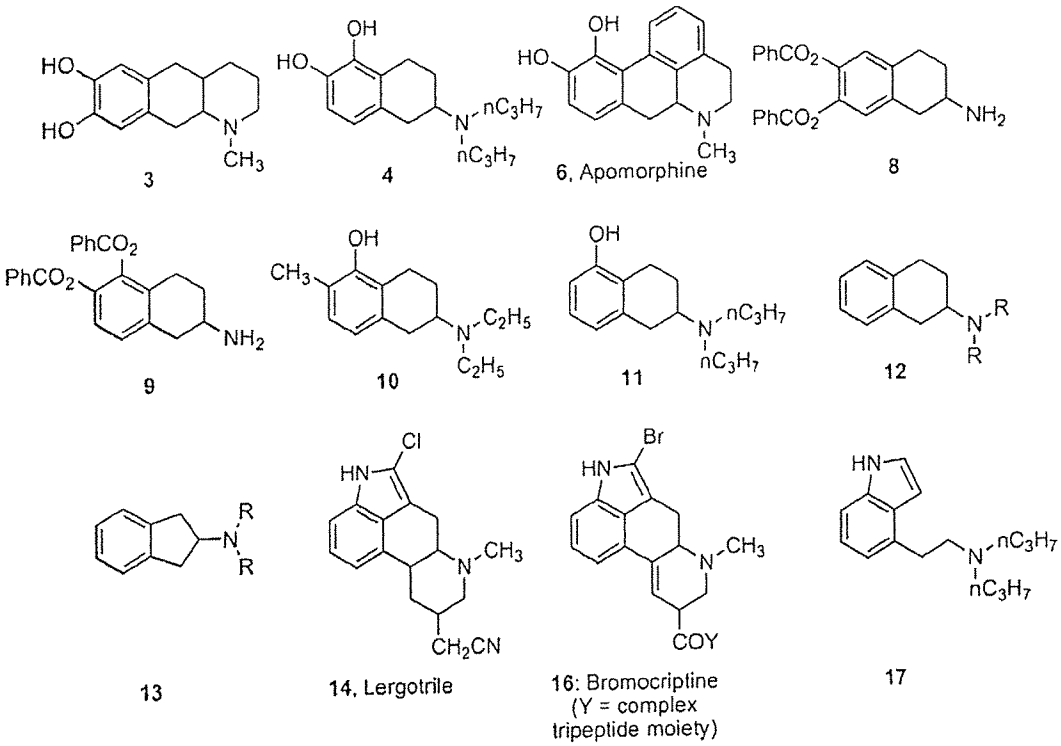
117. The biological activity of Compound 9 is based on hydroxylation of the compound *in vivo*.

d) *Not Obvious To Modify Compound 9 Or The '944 Patent Compound*

118. Teva's obviousness theory suggests that the compound described in the '944 patent or compound 9 of the Cannon 1981 article would have been natural starting points for a person of ordinary skill in the art having no knowledge of ropinirole, and that it would have been obvious to such a person to modify these compounds over other possibilities.

119. The 1981 Cannon Review article shows that, at the time of the invention, there were numerous structural classes of compounds with reported dopaminergic properties. This review article depicts a number of examples of dopamine agonists, encompassing a wide variety of

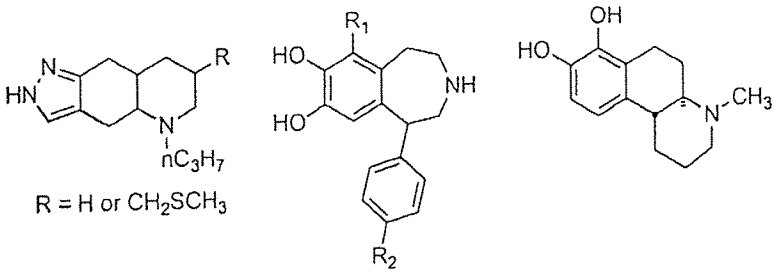
molecular frameworks, as shown below (numbering scheme from the article):



120. The Cannon 1982 Review article does not depict an indolone framework, nor does it even suggest an indolone framework.

121. Additional compounds with dopaminergic activity were depicted in summary articles published in the 1981 volume of *Annual Reports in Medicinal Chemistry*. Remy & Martin, Antipsychotic agents and dopamine agonists, *Ann. Rep. Med. Chem.* 16, 11-20, (1981); Dolak & Goldberg, Renal Blood Flow and Dopaminergic Agonists, *ibid.* 16, 103-111, (1981). Along with ergot alkaloid derivatives related to **14** and **16** above and aminotetralins like **4**, **10**-**12**, these reviews show examples of other ring systems with dopamine agonist activity, but do

not show an indolone system:



122. In suggesting that it would have been obvious to modify the indole of Compound 9 to make ropinirole, Teva ignores the chemical and structural differences between an indole and an indolone. These include: a ketone at position 2 in the indolone compound versus a carbon-carbon double bond between positions 2 and 3 in the indole; the indole is aromatic whereas the ketone of the indolone destroys the aromatic character of the nitrogen containing ring; the acidity of the hydrogen attached to the nitrogen is increased, because of the influence of the ketone group on the nitrogen, making it more available for hydrogen bonding to the receptor; the overall electronic character is altered in the molecule; and the lipophilicity is changed.

Moreover, the ring nitrogen of the indole would not be bioisosteric with a catechol hydroxy group. The indole lacks the ketone group at position 2 and the double bond is not sufficiently strong to withdraw electron density away from the nitrogen, which is what activates the hydrogen for hydrogen bonding to the receptor, and in fact results in the nitrogen being a hydrogen acceptor; thus reducing its ability to bond with the receptor.

123. Drs. Cannon and Long were clearly above ordinary skill in this art, were interested in improved dopamine agonists, and -- more than anyone else -- had the opportunity to consider

modifications to the indole derivative they were studying. Yet, they did not *then* come up with what they *now* seek to characterize as the "obvious" indolone structure of ropinirole. Moreover, they never attempted any modifications to an indolone structure to make a dopamine agonist.

124. In suggesting that it would have been obvious to modify the indolone compound of the '944 patent to make ropinirole, Drs. Cannon and Long also ignore the overall state of the art at the time of the invention of the '808 patent. Event after the filing of the '808 patent application, the hydroxy indolone structure from the '944 Patent was not mentioned in an extensive review article that Dr. Cannon published in 1983 (Cannon, J.G. Structure-activity relationships of dopamine agonists. *Annu. Rev. Pharmacol. Toxicol.* **23**, 103-129 (1983)), which covers a group of chemical structures with dopaminergic activity that is even larger than his earlier review. Nor was it mentioned in the updated overview of the field published that year in *Annual Reports in Medicinal Chemistry*. De Paulis & Läkemedel, *Ann. Rep. Med. Chem.*, **18**, 21-29 (1983). Drs. Cannon and Long fail to point to any teaching in the art that would have motivated a person skilled in the art at the time of the invention to select the '944 patent compound as a starting place for further experimentation.

125. For the above reasons, Teva has failed to demonstrate that, at the time of the invention, it would have been *obvious* to modify either the Huffman compound or compound 9 from the 1981 Cannon article to make ropinirole hydrochloride. Further, Teva has failed to demonstrate that, at the time of the invention it would have been obvious even to try to do so. "Obvious to try" is not a proper test of obviousness.

e) No Reasonable Expectation Of Success

126. Teva has also failed to demonstrate that a person of ordinary skill in the art would

have expected that any such modification would result in a compound suitable as a pharmaceutical candidate.

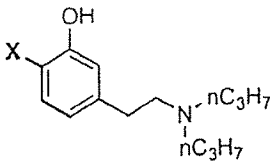
127. No prior art reference showed that the inclusion of a hydroxy group at the 7-position of an indolone compound was unnecessary for the compound's activity. No indolone compounds from which this comparison could be made had been reported in the prior art. To the extent any conclusion could be drawn from non-indolone compounds, it would have been that a hydroxy group at the 7-position of an indolone compound *was* necessary.

128. As discussed above, a hydroxy group at the 7-position is what makes an indolone a catechol mimetic. The understanding regarding the importance of having a catechol or a structure that mimicked a catechol was widespread, with leading dopamine researchers proposing that a dopamine agonist either had to have a catechol-like structure or had to be metabolically altered in the body to produce a compound with such structure. For example, Schmidt et al. observed that the "catechol nucleus appears essential for renal vascular dopaminergic activity." Schmidt, M., Imbs, J.L., Giesen, E.M. & Schwartz, J. Vasodilator effects of dopaminomimetics in the perfused rat kidney. *Eur. J Pharmacol.* 84, 61-70 (1982).

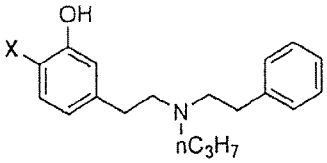
129. Teva points to several references in which compounds lacking an OH group have some biological activity. However, because the references relied on by Teva do not compare hydroxylated and dihydroxylated versions of the same compound, no meaningful conclusion can be drawn from them with respect to the importance of the hydroxyl group.

130. For example, the Geissler article cited by Drs. Cannon and Long describes a variety of central and peripheral effects of 3-(2-dipropylamino-ethyl)phenol on rats and mice and concludes that this molecule is a selective dopamine agonist. These effects were not compared

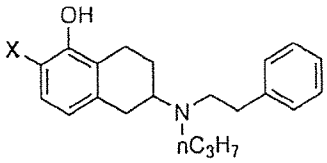
to those of the dihydroxy compound (X = OH), hence Geissler's results do not indicate whether removal of the hydroxyl group improves the activity, decreases the activity, or alters the selectivity of the molecule. Geissler also did not test the effect of removing the meta hydroxy and leaving the para hydroxy, which would have indicated which hydroxy group was of more importance.



X = H: Geissler's compound
X = OH: (dihydroxy analog)



X = H: Sumner's compound e
X = OH: (dihydroxy analog)



X = H: Sumner's compound g
X = OH: (dihydroxy analog)

131. In the Sumners article, five compounds related to the dopamine structure were evaluated for their ability to induce stereotypy in rats, their effects on dopamine metabolism, and their ability to antagonize the increase in striatal dopamine caused by gammabutyrolactone. Along with Geissler's compound, these authors studied the 2-phenylethyl-substitued analog e and the aminotetralin g shown above. However, the corresponding dihydroxy analogs (X = OH) were not studied, so the specific effect of this structural change could not be discerned from this publication either. Moreover, Sumners studied an additional compound (labeled **d**) that lacked a para hydroxy group and found the compound to be inactive at dopamine receptors

132. Relevant comparisons between dihydroxy-substituted analogs (compounds having two hydroxy groups) and monohydroxy-substituted analogs (compounds having only one hydroxy group, i.e., non-catechols) were in fact available in the prior art. For example,

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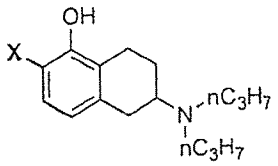
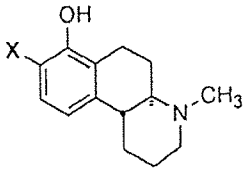
McDermed et al. report that the monohydroxy analog (±)-4 (depicted below) had only 1/7 the potency as an emetic in the dog and was only 1/3 as active in inducing stereotyped behavior in the rat as the dihydroxy compound (±)-1. McDermed, J.D., McKenzie, G.M. & Freeman, H.S. Synthesis and dopaminergic activity of (+/-)-, (+)-, and (-)-2-dipropylamino-5-hydroxy-1,2,3,4-tetrahydronaphthalene. *J. Med. Chem.* **19**, 547-549 (1976). Cannon et al. compare the activity of several tricyclic compounds, including **36** and **40**, in inducing *emesis* in dogs; in this series, the monohydroxy compound **36** was 200-fold less active than the dihydroxy compound **40**. Cannon, J.G. & Hatheway, G.J. Centrally acting emetics. 10. Rigid dopamine congeners derived from octahydrobenzo[f]quinoline. *J. Med. Chem.* **19**, 987-993 (1976). Neumeyer et al. evaluated the dopaminergic activity of the monohydroxy analog, **3e**, in comparison to apomorphine, in inducing rotational behavior in a rat model. Neumeyer, J.L. & Granchelli, F.E. Aporphines. 11. Synthesis and dopaminergic activity of monohydroxyaporphines. Total synthesis of (plus, minus)-11-hydroxyaporphine, (plus and minus)-11-hydroxynoraporphine, and (plus, minus)-11-hydroxy-N-n-propylnoraporphine. *J. Med. Chem.* **17**, 1090-1095 (1974). They found that **3e** produced a less pronounced effect than the dihydroxy compound apomorphine, even at 40 times the dose. Rather than implying any advantage or even equivalency of the replacement of hydroxyl with hydrogen, such references teach away from the suggestion that it would have been obvious to one skilled in the art who sought an improved dopaminergic agent to make an indolone lacking a hydroxy group.

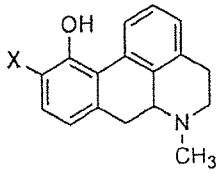
EXHIBIT 20 TO PROPOSED PRETRIAL ORDER



X = H: McDermed's cmpd (±)-4
X = OH: McDermed's cmpd (±)-1



X = H: Cannon's cmpd 36
X = OH: Cannon's cmpd 40



X = H: Neumeyer's cmpd 3e
X = OH: Apomorpine

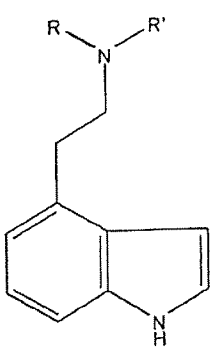
133. Other references also teach away from any suggestion to create an indolone lacking a catechol structure.

134. As discussed above, the dopamine agonist effects of Compound 9, the principle piece of prior art relied on by Teva, are due to their metabolism in the body to hydroxylated derivatives.

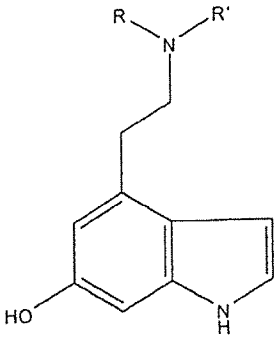
135. Similarly, the ergot derivatives bromocriptine and lergotrile also were thought to form hydroxylated metabolites that led to their dopamine agonist activity in vivo. (See Jenner, P., Marsden, C.D. & Reavill, C. Evidence for metabolite involvement in bromocryptine-induced circling behaviour [Proceedings]. *Br. J. Pharmacol.* **66**, 103P-104P (1979); Silbergeld, E.K., Adler, H., Kennedy, S. & Calne, D.B. he roles of presynaptic function and *hepatic drug metabolism* in the hypothermic actions of two novel dopaminergic agonists. *J Pharm. Pharmacol.* 29, 632-635 (1977); Parli, C.J., Schmidt, B. & Shaar, C.J. Metabolism of lergotrile to 13-hydroxy lergotrile, a potent inhibitor of prolactin release in vitro. *Biochem. Pharmacol.* **27**, 1405-1408 (1978) (showing that the 13-hydroxyderivative of lergotrile was a more potent agonist, as judged in receptor binding assays, than the parent molecule). For example, the 1979 Cannon article acknowledges that the dihydroxylated metabolite of Lergotrile (compound **21** in

this paper) was known to be a more potent agonists than lergotrile itself. Cannon, J.G., Dopamine congeners derived form the Benzo(f)-quinoline Ring. *Adv. Biosci.*, 20, 87-94 (1979).

136. In their 1984 paper, Drs. Cannon and Long themselves confirmed their earlier observation that only a hydroxylated form of their Compound 9 was "a potent dopamine receptor agonist in isolated cat atrial preparations." In fact, the unhydroxylated compound itself was "inactive as an agonist, being rather a weak antagonist" (*J. Med. Chem.* 27, at 388).



Compound 9
(Indole)



Compound 9
Active Metabolite

137. Although the position of hydroxylation of these compounds, like Compound 9, was proposed to be meta to the nitrogen, these observations were not supportive of the hypothesis that hydroxyl substitution was irrelevant to the activity of the indole or ergoline derivatives. Indeed, in 1982, Drs. Cannon and Long noted that others had suggested that compounds such as lergotrile actually were metabolized at the para hydroxy position to form catechol-like compounds. Cannon, J.G., J. P. Long, and B. J. Demopoulous, Indole-derived fragments of ergot alkaloids as dopamine cogeners, *Adv. Biosci.*, 189-199 (1982). These articles, to the extent that they taught anything about indolones, would have taught one skilled in the art that the hydroxyl group was necessary.

138. Further, the SAR that Cannon relies on in his expert report (that Compound 9 is the pharmacophore for ergoline derivatives) was only one of a number of different - and competing - hypotheses about the structural requirements of a drug to function as a dopamine agonist at the dopamine receptor. For example, Bach and Kornfeld proposed that the rigid pyrroleethylamine moiety of the ergolines is the portion responsible for dopamine agonist activity, and not the phenethylamine moiety suggested by Cannon. (Bach, N.J. *et al.* Bicyclic and tricyclic ergoline partial structures. Rigid 3-(2-aminoethyl)pyrroles and 3- and 4-(2-aminoethyl)pyrazoles as dopamine agonists. *J Med Chem.* **23**, 481-491 (1980); Clemens, J.A. et al. Stimulation of presynaptic dopamine autoreceptors by 4-(2-di-n-propylaminoethyl) indole (DPAI). *Life Sci.* 34, 1015-1022 (1984)). The person of ordinary skill who accepted Bach and Kornfeld's proposed SAR of the ergolines would not have looked to this chemical class as related to indolones and, in fact, would have been led away from the indolones altogether.

139. Dr. Cannon himself offered a candid contemporaneous assessment of the unpredictable state of the art with respect to SAR correlations among dopaminergic compounds (Cannon, J.G. The Design of Potential Anti-Parkinsonsian Drugs: What is the Dopaminergic Pharmacophore in Ergot Alkaloids? *Proc. Iowa Acad. Sci.* **93**, 169-174 (1986)):

> Probably many, if not most, of the dopaminergic agonist structure-pharmacology correlations that have been made in the past (by us and by others) are naive and do not necessarily reflect the true nature of dopaminergic agonist-receptor interactions, even though we can frequently use these correlations rationally to design biologically active compounds. . . . Moreover, a multiplicity of these different agonist-receptor complexes is capable of eliciting a physiological dopaminergic response. Different chemical series of dopaminergic agonists may be interacting with the same geographic areas on the receptor protein molecule but, depending upon the chemical nature of the specific chemical series of agonists, a different conformation of the receptor protein may be

> involved. Thus, within a *given chemical series* of agonists, there may be a well defined structure-activity and stereochemical correlation. But, these correlations may disappear when a different chemical series of agonists is addressed, and a new combination of structural parameters and stereochemical requirements may apply. If this be true, structural comparisons and correlations between ergoline derivatives, apomorphine derivatives, and other dopaminergic agonist molecular systems may not only be meaningless, but actually may be misleading. (from page 173, emphasis in original)

140. In 1988, Cannon further acknowledged that a single SAR for dopamine agonists may not exist:

> It may not be possible (nor, indeed, valid) to attempt to define a single structure-activity relationship for all dopaminergic agonists; it may not be valid to attempt to establish chemical and steric parameters for a dopamine receptor which will accommodate all chemical varieties of dopaminergic agonists that have effects at that receptor. If these ideas are valid, future structure-activity studies of dopaminergic agonists will be more difficult and challenging. However, the possibility of creating improved therapeutic agents with greater potency and specificity of action makes the endeavour eminently worth doing.

Cannon, J.G. Pharmacology and Functional Regulation of Dopaminergic Neurons. Beart, P.M., Woodruff, G.N. & Jackson, D.M. (eds.), pp. 1-8 (Macmillan Press, London,1988).

141. For the forgoing reasons, Teva has failed to demonstrate that a person modifying either the Huffman compound of the '944 patent or "Compound 9" of the Canon 1981 review article to make ropinirole hydrochloride would have had a reasonable expectation that the resulting compound would have been suitable as a pharmaceutical agent.

f) Secondary Considerations of Non-Obviousness

142. REQUIP was first approved in the United States on September 19, 1997, for the

treatment of Parkinson's disease. PTX 423, Ex. 1 to the Proposed Pretrial Order, ¶ 10. REQUIP was initially introduced as an adjunctive treatment (add-on drug) for Parkinson's disease patients who were having response problems to levodopa. REQUIP is among the drugs recommended by the American Academy of Neurology in its practice parameter for management of motor fluctuations in Parkinson's disease as an adjunctive therapy with levodopa.

143. REQUIP can also be used as an effective initial monotherapy (stand-alone treatment) for Parkinson's disease. As demonstrated in a clinical study published in the New England Journal of Medicine in 2000, known as "the 056 study," early Parkinson's disease can be managed for up to five years with REQUIP as initial therapy. A total of 34% of patients took REQUIP as their only medication for five years.

144. In certain instances, REQUIP offers advantages over pramipexole, the other non-ergoline dopamine agonist. REQUIP is eliminated from the body by hepatic metabolism (metabolized predominately in the liver), while pramipexole is eliminated by the kidney. Depending on a particular patient's medical conditions, one or the other of these drugs may be indicated. For example, ropinirole can safely be given to renal failure patients without dosage adjustment.

145. Another advantage of REQUIP is its broad *dynamic range* (the dose range across which the drug can be used). The dynamic range of REQUIP is larger than that of pramipexole. REQUIP's dosage can often be increased with incremental benefit and in high dose ranges, ropinirole is more effect and better tolerated than pramipexole.

146. Prior to the approval of Requip, there was a long felt need for additional methods of treating Parkinson's disease. Requip fulfilled this need.

EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

147. Restless Legs Syndrome ("RLS") is a movement disorder, the symptoms of which manifest themselves in several different ways. Some patients with RLS have an irresistible urge to move their legs when sitting or laying down. Other symptoms include a burning, creeping, crawling, or tingling sensation in the legs that is sometimes described as feeling like insects crawling inside the legs. Symptoms are worse later in the day and at night; lying down and going to sleep usually activates the symptoms, thereby causing severe sleep disruption. If left untreated, the condition may contribute to exhaustion and daytime fatigue, which can detrimentally affect one's job, personal relations, and daily activities. Up to 5-10% of the adult population may suffer from RLS.

148. REQUIP received priority review from the FDA and was approved for the treatment of RLS in May 2005. PTX 237, 298, 419. It is the first and only drug approved for treatment of RLS. This approval is evidence of REQUIP's safety and efficacy.

149. Prior to the approval of REQUIP for the treatment of RLS, there was a long-felt medical need for an approved treatment of this condition. REQUIP fulfills this need.

REDACTED

EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

REDACTED

154. REQUIP has been commercially successful.

155. The commercial success of REQUIP is due, in significant part, to use of the inventions claimed in the '808 patent in the production and sale of REQUIP. The '808 patent covers the active compound that delivers to a patient the benefits afforded by REQUIP. Absent use of the inventions claimed in the '808 patent, its sales would not have been possible. While other dopamine agonists are on the market, a substantial set of physicians and patients have concluded that REQUIP offers a preferred treatment option. Many of them choose to initially prescribe and purchase REQUIP, and then continue to do so.

G. Enforceability Of The '808 Patent

156. Teva's claim with respect to the enforceability of the '808 patent asserts four allegations of inequitable conduct:

a. Mr. Gallagher committed inequitable conduct with respect to the '808's generic patent claims because he was not entitled to be an inventor of those claims.

b. The '808 patent falsely states that ropinirole does not cause tachypylaxis.

c. The '808 patent falsely suggest that ropinrole hydrochloride was tested in humans.

d. Dr. Paul Hieble, a GSK pharmacologist, should have been named as an inventor, but was intentionally not named as an inventor to prevent the disclosure of allegedly material prior art of which Dr. Hieble was aware.

EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

1. Breadth Of Generic Claim

157. Inventors in a pharmaceutical company, as elsewhere, have varying degrees of familiarity with the patent prosecution process. Inventors are very rarely lawyers or patent agents and, therefore, naturally rely on the advice and judgment of the lawyers or patent agents responsible for obtaining patent protection for the invention.

158. Among the duties of the patent practitioners before the United States Patent & Trademark Office is the obligation to obtain the broadest claims possible under Title 35, consistent with the disclosure of the patent application, the scope of the prior art of which he or she is aware, and the duty of candor. Accordingly, prosecuting attorneys are trained to draft and seek to obtain, broad, generic claims, which fairly reflect the contribution of the inventor to the art. In doing so, they routinely seek and are granted protection beyond the specific embodiment(s) discovered or developed by the inventor. See, e.g., Robert C. Faber, *Landis on Mechanics of Claim Drafting*. § 10:1.1, 5th Ed., 2005 ("Broad coverage means not only that every particular preferred disclosed embodiment is protected in the claims, but that the claims cover all expected and unanticipated equivalents that competitors and others may later develop and all intentional and unintentional copies of the claimed invention which embody the inventor's concept. The inventor/client will compare a competitive or a similarly functioning product or process with the patented embodiments. If the client sees similar structure, operation and/or result, he will want to be able to use his patent to halt an infringement. It is the claim drafter's job to have written the claims in the application to not only cover what the attorney and the inventor/client could at the time of application prosecution have envisioned as competing products, but to cover competitive products which neither the inventor nor the attorney thought

of or could even have imagined at the time, but which employ the concept of the invention."); Jeffrey G. Sheldon, *How to Write a Patent Application*, Practicing Law Institute, § 6.5, 2006 ("The broadest claim should be as broad as possible in view of the prior art. As long as the broad claim is not anticipated by art known to the inventor, it cannot hurt to ask for the broad claim. At worst, the examiner will not allow the broadest claims. Thus, it is recommended that the practitioner be greedy when initially writing the application."); Irving Kayton, *Kayton on Patents*, 2nd ed., 3-1, 1983 ("During the prosecution stage the drafter will naturally attempt to write one claim that is as broad as the prior art of which he is aware will permit and that is supported by the disclosure in his patent application.").

159. With respect to chemical patents in particular, a patent limited to the precise compounds reduced to practice by an inventor would frequently be of little or no value because of the ability to obtain the same functionality of the compound by making minor substituent variations or manipulations to the molecule. Thus, it is normal and customary practice for a patent attorney to draft a patent application to include generic formulas that would include any related substituents that could reasonably be expected to exhibit similar activity, and to seek claims to such generic formulas. This does not make the inventor of the chemical compound any less the inventor of the generic formula. Rather, invention of the specific compound entitles the inventor to a *genus* of compounds of reasonable scope.

160. A genus or generic claim is one that covers more than a single chemical compound. It is typical for a patent attorney or agent to more broadly claim the invention to include other *species* that are envisioned to have the same utility and can be similarly made in order to ensure that the invention is protected. This broadened concept becomes the genus in a patent

application.

161. The existence of only one working example or even the possibility of inoperative species does not automatically result in the genus claim not meeting the statutory requirements. It is acceptable for a specification to merely contain a written description of the broadly claimed invention without having to, in addition, detail every species that is encompassed by such a genus claim.

REDACTED

163. Mr. Gallagher was involved in determining the scope of claim 1.

164. The specification of the '808 patent describes a way to synthesize ropinirole and provides data supporting its utility. The '808 patent also provides several prophetic examples of the synthesis of related compounds other than ropinirole coming within the generic formula. In light of the disclosure of the '808 patent and the disclosure of the '944 patent (which is cited in the '808 patent as prior art), the generic claim sought by the applicant in the '808 patent is reasonable

165. No objection was made by the examiner that any species within the genus claim of the '808 patent did not have utility. This is consistent with the Manual of Patent Examining Procedure's ("MPEP") guidance for patent examiners when considering the scope of generic claims:

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> With respect to the adequacy of disclosure that a claimed genus possesses an asserted utility representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if it would be deemed likely by one skilled in the art, in view of contemporary knowledge in the art, that the claimed genus would possess the asserted utility. Proof of utility will be required for other members of the claimed genus only in those cases where adequate reasons can be advanced by the examiner for believing that the genus as a whole does not possess the asserted utility.

MPEP § 608.01(p) at pp. 102-3 (4th ed., rev. Sep. 1982) (citations omitted).

166. The patent examiner who examined the '808 patent had before him the genus disclosed in the '944 patent, which had been cited to the PTO by the applicant and which was the closest prior art. Given this disclosure, it would have been reasonable to conclude that the claimed genus of the '808 patent would possess the asserted utility.

167. Mr. Gallagher did not fail to disclose any material information with respect to the invention of the genus claims of the '808 patent.

168. There is no evidence of an intent to deceive the Patent Office concerning inventorship of the generic claims of the '808 patent.

2. Statement Regarding "Tachyphylaxis"

169. The '808 patent states: "In addition to not having a catechol or catechol-mimicking structure, these indolones may not be subject to tachyphylaxis [drug tolerance] and are better absorbed orally when compared with the prior art compounds based on preliminary pharmacological tests with the preferred species of this invention."

170. This statement is true.

REDACTED

171. The statement in the patent concerning tachyphylaxis is immaterial. Patentability of the compounds claimed in the '808 patent rested on their unexpected cardiovascular activity. See, e.g., '808 Patent, col. 1, lines 40-43. The existence or non-existence of tachyphylaxis was never a subject of prosecution, and is not suggested as a basis of patentability in the specification.

172. There is no basis for inferring any intent on the part of GSK to mislead the patent office. REDACTED . Yet, there is no requirement that an inventor have personal knowledge of or verify every statement in a patent application. The statement in the patent specification that no tachyphylaxis was observed in a particular experiment is indisputably true, and there is no evidence that Mr. Gallagher thought otherwise or knew of evidence to the contrary.

3. Effective Dose In Humans

173. As is typical in pharmaceutical patents, the '808 patent includes information concerning possible doses. The entire discussion of dose in the '808 patent is as follows:

> Advantageously, doses selected from the dosage unit ranges given above will be administered several times, such as from one to five times, a day. The daily dosage regimen is selected from the range of about 50 mg to about 1.0 g, preferably 200-750 mg for oral administration and 50-500 mg for parenteral administration. When the method described above is carried out, D2 -agonist activity is produced.
>
> For an average size human using 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride as an active ingredient, a typical dose to show anti-hypertensive activity would be selected from the range of from about 100-250 mg of base equivalent for each dosage unit which is adapted for oral administration and which is administered orally from 1-4 times daily.

'808 Patent, col. 5, line 59 - col. 6, line 5.

174. According to Teva, this passage falsely "suggests" that actual human testing was performed to determine the disclosed range of doses.

175. Even if a "suggestion" could ever give rise to an inequitable conduct claim, there is no support for Teva's claim that the '808 patent would lead any person skilled in the art to believe that the quoted passage implied actual human testing.

176. First, this passage is from the section of the '808 patent under the heading "Description of the Invention," and is not one of the nine numbered Examples that follow, starting at col.6, line 11 through col. 10, line 12. The passage comprises part of the '808 patent description of the pharmaceutical compositions of the invention, which begins at col. 4, line 63, and includes six full paragraphs, of which the passage comprises two paragraphs, and which ends at col. 6, line 5.

177. Neither the passage cited by Teva, nor the larger passage of which it is a part, is presented as an example of actual human testing, nor could either be fairly read to suggest that actual human testing had been performed. Throughout the larger passage, a mix of present, future and subjunctive tenses is properly used, and indicates to the reader that the description of the pharmaceutical compositions, the preparation of dosage forms, the pharmaceutical carrier employed, the form of the pharmaceutical, the route of administration, the daily dosage regimen and the typical dose, does not reflect actual human testing, in accordance with accepted patent application drafting principles.

178. That the passage cited by Teva, as well as the larger passage, is not included as one of the Examples is further evidence that no reasonable reader would reach the conclusion that it

amounted to a false suggestion that human testing had been performed, as Teva suggests.

179. Even if this passage were somehow divorced from the context of its larger passage and considered to be an example, it would clearly be understood to be a prophetic example. In the drafting of patents, the distinction between actual "working" examples and "prophetic" examples is well established. Working examples describe tests that have actually been conducted. MPEP § 608.01(p) at 104. (Simulated or predicted test results and prophetical examples (paper examples) are permitted in patent applications . . . Paper examples describe the manner and process of making an embodiment of the invention which has not actually been conducted.). Working examples typically use the past tense to describe the actual work performed, while "[p]aper examples should not be described using the past tense. *Hoffman-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1367, 66 USPQ2d 1385, 1394 (Fed. Cir. 2003)." MPEP § 608.01(p) at 1600-99 (8th ed., rev. Aug. 2006).

180. In the '808 patent, the information describing dose is in the future and subjunctive tense: "Advantageously, doses selected from the dosage unit ranges given above will be administered several times," "[t]he daily dosage regimen is selected from the range of about 50 mg to about 1.0 g," "[f]or an average size human using 4-(2-di-n-propylaminoethyl)-2(3H)-indolone hydrochloride as an active ingredient, a typical dose to show anti-hypertensive activity would be selected from the range of from about 100-250 mg."

181. In addition, a new chemical compound that is the subject of a pharmaceutical patent application would often and most likely not have been actually tested in humans at the time the application was filed. The Hatch-Waxman Act -- the federal statute that is the basis for ANDA filings such as the Teva ANDA at issue in this proceeding -- also provides for patent term

extension precisely because of the loss of patent life due to FDA-required human clinical testing. Yet, a pharmaceutical company must file its patent application at an early stage or run the risk that others may publish on the company's compounds and impair future patent rights abroad where jurisdictions follow "a first to file" system. Thus, a patent examiner would understand that the actual results of human testing would typically be available only for a second or third generation improvement for which patent protection is sought to an existing patented compound.

182. The '808 patents statements concerning expected dose were not false. Teva has not introduced any evidence showing that Mr. Gallagher or anyone else at GSK believed that the expectation recited in the '808 patent was not, in fact, what GSK expected.

183. The discussion of dose was not material to the prosecution of the '808 patent because any patent examiner would have understood that human trials would not have commenced at that time in the development of a new pharmaceutical compound. Dose ranges were not a subject of prosecution of the '808 patent or a basis of patentability.

184. Neither Mr. Gallagher nor anyone else at GSK intended to deceive the Patent Office with respect to the dosing information provided in the '808 patent.

4. Improper Inventorship

185. Teva contends that Dr. Hieble should have been named as an inventor of the '808 patent and that he was not named as inventor for the express purpose of avoiding disclosure of the 1981 Cannon Article.

186. There is no basis for concluding that Dr. Hieble should have been an inventor. He was not responsible for conceiving ropinirole, nor was he involved in its synthesis or the initial decision to test it for biological activity.

187. Dr. Hieble was not involved in the prosecution of the '808 patent.

188. Teva has failed to show that Dr. Hieble knew of the existence of the 1981 Cannon Article during prosecution of the '808 patent.

189. Teva has failed to show that anyone involved in the prosecution of the '808 patent knew of the 1981 Cannon Article.

190. Teva has failed to show that someone involved in the '808 prosecution knew that Dr. Hieble had knowledge of undisclosed prior art.

191. For the reasons stated in the discussion of obviousness, the 1981 Cannon Article is immaterial to patentability.

192. Teva has failed to show that there was any intent to deceive the Patent Office with respect to the 1981 Cannon Article.

H. Validity Of The '860 Patent

1. Non-Obviousness of '860 Patent

a) The Level of Skill In The Art

193. At the time of the invention, Dr. Owen had not specialized in dopaminergic compounds.

194. In 1987, pharmacologists at GSK were not segregated by chemical compound. To the extent that there was specialization within pharmacology at that time, it was a focus on a type of disease or an organ system instead.

195. A person of ordinary skill in the art at the time of the invention of the '860 patent (1987) would have been an individual with an advanced degree (M.S. or Ph.D.) in organic chemistry or pharmacology and having two or three years of laboratory experience in

pharmacology in an academic or industry setting. A person without a graduate degree, but having more laboratory experience in this field, could also be considered a person of ordinary skill at the time of the invention.

b) **The Content Of The Art**

196. In its expert reports, Teva identifies the following references as purportedly rendering claim 5 of the '860 patent anticipated or obvious.

a. The '808 patent;

b. The '808 patent in combination with Compound 9, as disclosed in the Cannon 1981 article and a 1986 article of Cannon;

c. The '808 patent in combination with a 1978 article of Cannon.

197. The '808 patent and Compound 9, as disclosed in the Cannon 1981 article, are discussed at length above. The 1986 article also discloses Compound 9 (identified therein as Compound 33) and suggests that it is the pharmacophore for ergot alkaloids known to treat Parkinson's Disease, such as lergotrile and pergolide. The 1978 article indicated that certain compounds, diethyl dopamine (compound 2) and di-*n*-propyl dopamine (compound 3), would "pass the blood brain barrier" and act as CNS dopaminergic agonists. In sum, Teva contends that knowledge that ropinirole was effective as a presynaptic D2 dopamine agonist in the peripheral nervous system would have led one of ordinary skill in the art to the conclusion that ropinirole would also be effective as a postsynaptic D2 dopamine agonist in the central nervous system.

c) It Would Not Have Been Obvious To Use Ropinirole As A Parkinson's Drug At The Time Of The Invention Of The '860 Patent.

i) Peripheral v. CNS Dopamine Agonists

198. In general, after determining that dopamine deficiency in the striatum was responsible for Parkinson's Disease, an era of discovery ensued in which drugs of many different chemical structures were synthesized in the hope that they would be as effective as levodopa in reversing the motor symptoms of Parkinson's Disease yet without unwanted side effects.

199. One major hindrance in developing dopamine agonists for the treatment of Parkinson's Disease or for other applications, such as use in cardiovascular disease, was that that the nature of the drug target, namely the dopamine receptor, was not well understood.

200. Prior to 1979, the general belief was that only one dopamine receptor existed. *See* Clement-Cormier Y.C., Parrish R.G., Petzold G.L. & Greengard P. Characterization of a dopamine-sensitive adenylate cyclase in the rat caudate nucleus. *J. Neurochem.* **25**, 143-149 (1975). At the same time, there was doubt over whether a single dopamine receptor could explain all the behavioural, pharmacological, and biochemical observations associated with dopamine receptors. In 1979, Kebabian and Calne published a paper demonstrating the existence of two classes of dopamine receptors. Kebabian, J.W. & Calne, D.B. Multiple receptors for dopamine. *Nature.* **277**, 93-96 (1979). These were termed D-1 and D-2 receptors.

201. In the years that followed, definitions and classifications of the types of dopamine receptor changed repeatedly as scientists attempted to understand their nature and function. Numerous schemes were proposed and rivalries among research teams existed until advances in molecular cloning allowed the adoption of a universal standard in 1998.

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202. The study of dopamine receptors was not limited to a single field of investigation in pharmacology. As the physiological function of dopamine systems and the pharmacological activity of dopaminergic drugs began to be understood, further research was pursued by entirely separate disciplines. These activities were, in general terms, focused on two areas of therapy. The first area of focus was within the discipline of cardio-vascular pharmacology. A cardiovascular pharmacologist would be interested in researching the actions of dopamine in peripheral tissues. The second area of focus was within central nervous system pharmacology. A CNS pharmacologist would pursue the actions of dopamine in the brain relevant to neurology and psychiatry. The relevant literature and knowledge, tools and research approaches were distinct enough that one of ordinary skill in cardiovascular pharmacology would not necessarily be skilled in central nervous system pharmacology and vice versa.

203. During the time period encompassing both patents, central dopamine receptors typically were referred to as D-1 and D-2 receptors, while peripheral receptors were termed DA-1 and DA-2. Kohli, J.D., Glock, D. & Goldberg, L.I. Selective DA2 versus DA1 antagonist activity of domperidone in the periphery. *Eur. J. Pharmacol.* **89**, 137-141 (1983).

204. At the time of the filing of the '860 patent, it was known that the nervous supply to organs and tissues in the peripheral parts of the body and the neuronal networks in the brain had vastly different functions. It was also understood that the action of agonists at peripheral and central dopamine receptors was not identical. In 1983, Dr. Arvid Carlsson, who would later be awarded a Nobel Prize for his work on dopamine, proposed that a dopamine agonist could have variable activity depending on the sensitivity and localization of the receptor. Carlsson, A. Dopamine receptor agonists: intrinsic activity vs. state of receptor. *J Neural Transm.* **57**, 309-315

(1983). According to Carlsson, a dopamine receptor that is naturally exposed to very low levels of the neurotransmitter will up-regulate and acquire a higher sensitivity to dopamine than a receptor exposed to a normally high level of dopamine. Because peripheral D-2 receptors are naturally exposed to only low levels of dopamine while dopamine D-2 receptors on target cells in the brain are continually exposed to high levels of dopamine, it was well known that agonists could exhibit a high intrinsic activity at peripheral D-2 receptors and a non-existent or even antagonistic activity at receptors on target cells in the brain.

205. At the time of the filing of the '860 patent, it was therefore widely believed that the brain and peripheral nervous systems contained different dopamine receptors. Accordingly, information derived from the study of peripheral dopamine receptors would not have been considered by the person of ordinary skill at the time to necessarily apply also to those receptors in the brain.

206. It was known that some compounds had been shown to have effects on dopamine receptors in either peripheral tissues or in the brain, but not on both. A fairly extensive body of literature at the time supported the view that an extrapolation from one location of dopamine D-2 receptors to another could have led one to an erroneous conclusion.

207. At the time of the filing of the '860 patent, a number of compounds were known to have activity on peripheral dopamine receptors, but not dopamine activity in the brain. Two such examples are (-)-3-PPP, which was developed in the early 1980s, and the ergot derivative trans-dihydrolisuride. In studies of these two compounds, researchers reported that both compounds were potent agonists on dopamine D-2 receptors present in the pituitary gland that controls prolactin secretion, but which is outside of the brain, but functioned essentially as

antagonists on D-2 receptors on target cells in brain. Carlsson, M., Carlsson, A. & Eriksson, E. The intrinsic activities of the partial dopamine receptor agonists (-)-3-PPP and TDHL on pituitary dopamine receptors are lower in female than in male rats. *Eur. J Pharmacol.* **142**, 39-43 (1987); Krejci, I., Schuh,J., Pragerova,H. & Dlabac,A. Lisuride and transdihydrolisuride: differences in action on central dopaminergic functions in dependence on the location and the state of receptors. *Pol. J Pharmacol. Pharm.* 37, 263-271 (1985). One of ordinary skill in the art also would have known that drugs such as fenoldopam, a D-1 agonist, acted on the renal vasculature, but did not penetrate into the brain. Goldberg, L.I. Dopamine receptors and hypertension. Physiologic and pharmacologic implications. *Am. J. Med.* 77, 37-44 (1984).

208. Other significant compounds were known at the time that were largely inactive in the peripheral nervous system but had potent activity in the brain. These compounds included ergot alkaloids and their derivatives, as well as piribedil, a drug shown to be effective in Parkinson's Disease. Goldberg, L.I. & Kohli, J.D. Dopamine Receptors. Kaiser, C. & Kebabian, J.W. (eds.), pp. 101-113 (American Chemical Society, Washington DC, 2006); Goldberg, L.I., Kohli, J.D., Kotake, A.N. & Volkman, P.H. Characteristics of the vascular dopamine receptor: comparison with other receptors. *Fed. Proc.* 37, 2396-2402 (1978); Wachtel, H., Dorow, R. & Sauer, G. Novel 8 alpha-ergolines with inhibitory and stimulatory effects on prolactin secretion in rats. *Life Sci.* **35**, 1859-1867 (1984).

209. However, not all ergot derivatives are useful in the treatment of Parkinson's Disease. For example, transdihydrolisuride and a compound from Sandoz labeled 208-912 were known not to exhibit significant agonist effects on dopamine receptors and would not be of benefit for the treatment of Parkinson's Disease. Coward, D.M. *et al.* Partial dopamine-agonistic

and atypical neuroleptic properties of the amino-ergolines SDZ 208-911 and SDZ 208-912. *J Pharmacol. Exp Ther.* **252**, 279-285 (1990).

210. Accordingly, even if ropinirole had been considered similar to ergot derivatives (which it was not, being a "non-ergot" agonist) such similarity would not have indicated that ropinirole could be used for the treatment of Parkinson's Disease.

211. Compounds that act on *presynaptic peripheral* dopamine receptors will not necessarily be active at *postsynaptic central* dopamine receptors. The 1978 Cannon Article relied on by Teva notes that a presynaptic peripheral compound has postsynaptic central behavior. Cannon, J.G. *et al.* Preparation and biological actions of some symmetrically N,N-disubstituted dopamines. *J Med Chem.* **21**, 248-253 (1978). However, this article does not discuss ropinirole or a compound like ropinirole, and even "tentatively" suggests that "requirements for peripheral and central dopamine receptor activation may differ . . . ." In addition, in the 1981 Cannon Review Article, Cannon noted that an aminotetralin labeled Compound 10 specifically interacted with both presynaptic peripheral and presynaptic central dopamine receptors but had little effect on postsynaptic receptors in either the periphery or in the central nervous system, as shown by the failure to induce stereotyped behaviour in rodents and emesis in dogs.

212. One of the obstacles to designing drugs intended to act on the central nervous system is the need for the drug, when taken internally, to cross "the blood-brain barrier." The blood-brain barrier controls the passage of substances from the blood into the central nervous system. Teva contends that it was known that the removal of the OH from the Huffman compound of the '944 patent would increase *lipophilicity* (the attraction of a compound to certain

organic compounds such as fats) and that this in turn would increase the ability of a compound to pass through the blood-brain barrier. However, at the time of the '860 patent, a person of ordinary skill would know that alterations in molecules acting on dopamine receptors to increase lipophilicity would not necessarily result in activity in the brain.

213. Highly lipophilic dopamine antagonists were known that were incapable of activity in the brain. For example, the dopamine antagonist domperidone is a highly effective antagonist at D-2 dopamine receptors in peripheral tissues. Because domperidone is lipophilic, it was initially hoped that it would cross the blood-brain barrier and, hence, function as a dopamine receptor antagonist in the brain. However, domperidone was shown not to be active on brain dopamine receptors, despite its lipophilicity. Laduron, P.M. & Leysen, J.E. Domperidone, a specific in vitro dopamine antagonist, devoid of in vivo central dopaminergic activity. *Biochem. Pharmacol.* **28**, 2161-2165 (1979).

214. Ropinirole was known as a peripheral dopamine agonist with cardiovascular effects and the report of initial tests carried out on the compound suggested that it did not have central behavioural effects. Accordingly, a person of ordinary skill in the art in 1987 would not have had a reasonable expectation that ropinirole would have a central nervous system effect and would therefore be effective as a Parkinson's drug.

ii) Behavioural Testing of Ropinirole Was Not Indicative of Actions of Ropinirole in PD

215. Many models of the effects of dopaminergic drugs on the cardiovascular system involve either isolated organs or anaesthetised animals. This fact makes it impossible to detect motor changes relevant to an action on the brain or to Parkinson's Disease because the animals

are not conscious and therefore no behaviour can be observed. When ropinirole was subjected to such tests, it was known to have a weaker interaction with the D-2 dopamine receptor than other dopamine agonists that had shown activity in Parkinson Disease. This fact would have not made it an obvious candidate to be advanced through the drug discovery process. In light of these data, it would not have been expected that ropinirole would be developed for use as a drug for treating Parkinson's Disease.

216. In his expert report, Dr. Cannon has also evaluated tests conducted by GSK and published in Gallagher, G., Jr. *et al.* 4-[2-(Di-n-propylamino)ethyl]-2(3H)-indolone: a prejunctional dopamine receptor agonist. *J Med Chem.* **28**, 1533-1536 (1985) ("the Gallagher Paper") on ropinirole, such as the *perfused rabbit ear artery, confinement motor activity* ("CMA"), *adenylate cyclase,* and *hexobarbital* testing, and concluded that a person of ordinary skill in the art would have concluded that ropiniorole would have been an effective Parkison's drug from this testing. In particular, he has stated that the confinement motor activity ("CMA") testing would have suggested that ropinirole would be an effective drug for treating Parkinson's disease and that the lack of effect on adenylate cyclase and hexobarbital sleep time test would not have led one away from developing ropinirole for Parkinson's disease.

217. With respect to the confinement motor activity model, one of ordinary skill in the art would have known that this test was not an established test of potential efficacy in Parkinson's disease. Rather, it would have been understood to be a behavioural model used as a routine screen to eliminate drugs that might exert unwanted effects that manifest themselves in an obvious change in behaviour, regardless of the *cause* of such effects.

218. Alterations in animal behaviour were known at the time to have many causes and

were not considered to be necessarily reflective of either activity in the brain or the involvement of brain dopaminergic systems. One of ordinary skill in the art, during this time period, would have recognized that inhibition of locomotor activity in a CMA test could be caused by the actions of many different pharmacological classes of drug or by *peripheral* actions unrelated to the dopaminergic system, for example cardiovascular changes, muscle relaxant activity, or the induction of pain. One of ordinary skill in the art would not have interpreted an inhibition of motor behaviour as indicative of a central dopaminergic action relevant to Parkinson's Disease.

219. This knowledge is reflected in the 1981 Cannon Article in which it is reported that Compound 9 decreased locomotor activity in rats. While noting that this could be the result of brain dopaminergic activity, the authors expressed uncertainty on this point noting that "some other mechanism" may be responsible. One of ordinary skill in the art in the 1980's would have known that similar results could be obtained if changes in the cardiovascular system had occurred and the animals had been treated with drugs falling into other pharmacological classes, such as sedatives, hypnotics, analgesics or neuromuscular junction blockers.

220. GSK researchers used the CMA test as an early screen for undesirable behavioural effects that might rule out ropinirole as a cardiovascular drug candidate at pharmacological doses producing the desired cardiovascular effects. Had such behavioural changes been observed in the CMA test, ropinirole presumably would have been rejected by those researchers as a potential cardiovascular drug candidate, irrespective of the mechanism responsible for the behavioural effects.

221. Testing for activity at brain dopamine receptors reported in the Gallagher paper actually would have been interpreted by those of ordinary skill in the art to show that ropinirole

does not have such effects. Cannon's conclusion that no inference can be drawn about activity at D-2 receptors in the brain from examination of its effects on adenylate cyclase is mistaken. The adenylate cyclase test can be used to determine whether a compound is a D-1 or a D-2 agonist. D-1 agonist compounds increase cyclic AMP formation whereas D-2 agonist compounds can decrease its formation. Stoof, J.C. & Kebabian, J.W. Opposing roles for D-1 and D-2 dopamine receptors in efflux of cyclic AMP from rat neostriatum. *Nature.* **294**, 366-368 (1981). This is because D-1 receptors are positively linked to adenylate cyclase as a second messenger system while D-2 receptors are negatively linked to the same transduction process. One prominent example of a centrally active compound that inhibits adenylate cyclase production is bromocriptine, which is an agonist at D-2 (although it also acts as an antagonist at D-1 receptors). If ropinirole had been shown to inhibit adenylate cyclase production, those of skill in the art would have recognized that ropinirole acted as an agonist at brain D-2 receptors. A person of ordinary skill therefore would have interpreted the fact that there was no effect on cyclic AMP as showing that under the conditions employed, ropinirole stimulated neither D-1 or D-2 receptors in the brain.

222. In addition, the use of hexobarbital sleeping time was known to be another routine test used in the drug development process to look for untoward central effects of molecules that would prevent their progression to becoming drugs. Potentiation of hexobarbital sleeping time was taken to indicate an additive but potentially adverse pharmacological effect on brain, and the lack of effect of ropinirole would have been taken by one of ordinary skill to indicate that it did not possess activity that would prohibit its development for other indications.

223. The testing of ropinirole disclosed by the Gallagher paper as having been

undertaken by GSK would not have led a person of ordinary skill in the art to have expected that ropinirole would have been effective as a Parkinson's drug.

2. Commercial Success

224. Claim 3 of the '860 patent encompasses the use of ropinirole for the treatment of Parkinsons Disease.

225. Ropinirole cannot be used for the treatment of Parkinsons Disease without practicing the inventions claimed in the '860 patent asserted by GSK. For the majority of the period during which REQUIP has been available, the treatment of Parkinsons Disease has been its central source of prescription volume. The commercial success of REQUIP is due in significant part to the inventions claimed in the '860 patent.

226. REQUIP was introduced in the U.S. in 1997, upon receiving FDA approval for the treatment of Parkinsons Disease. Prior to 2005, the only indication for which REQUIP had FDA approval was Parkinsons Disease. Thus, except for off-label use, all of the sales and profits associated with REQUIP through early 2005 (and a substantial portion thereafter) are attributable to the inventions claimed in the '860 patent.

227. Available data indicate that REQUIP's use "off-label" for the treatment of RLS constituted a small proportion of REQUIP prescriptions through at least mid- 2004. Furthermore, even in 2005 and 2006 (during which time REQUIP was also approved by FDA for the treatment of RLS), significant portions of REQUIP's sales were for the treatment of Parkinson's Disease.

228. REQUIP, as used to treat Parkinson's disease, has been a commercial success.

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3. Validity Under § 102(f)

229. Teva asserts that claim 3 of the '808 patent is invalid under 35 U.S.C. §102(f) because the claimed invention was derived from the work of Bradford University.

230. Dr. Owen was the first to conceive using ropinirole as an anti-Parkinson's Disease drug. He communicated this invention to Bradford University, whose testing was merely confirmatory of Dr. Owen's invention.

231. The claimed invention was not derived from the work of Bradford University.

I. Enforceability

1. Inventorship

232. According to Teva, "[p]laintiffs' nonjoinder of individual(s) responsible for conceiving of portions of the claimed inventions(s) covering compounds other than ropinirole or its hydrochloride salt was done with the intent to deceive the PTO so that the '860 patent would be issued." Corrected Amended Complaint ¶ 60.

233. The '860 patent does not suggest that any compound other than ropinirole had been actually tested for its anti-Parkinson's disease effect. As with the '808 patent, GSK was nonetheless entitled to a genus claim of appropriate scope. The generic claim of the '860 patent that was sought and obtained by GSK is reasonable in light of the disclosure of the '860 patent and the prior art.

234. Given the teaching of the '944 and '808 patents, it would have been reasonable to seek a genus claim in the '860 patent of substantially the same scope as the '808 patent and the '944 patent. However, the genus in claim 1 of the '860 patent is narrower at the 4-position than the genus claimed in the '944 or '808 patents as shown in the chart below comparing the genus

claims of these patents. The genus of claim 1 of the '860 patent is also narrower than the genus of the '808 patent at the 1-position as shown below. In the '860 patent, hydrogen is bound to the indole nitrogen ring, whereas in the '808 patent there may be either hydrogen or a lower-alkyl substituent bound to the indole nitrogen ring.

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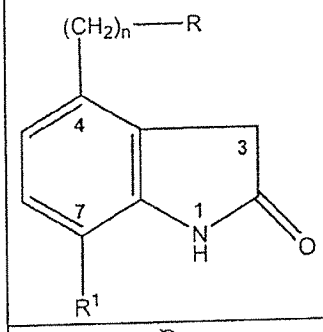
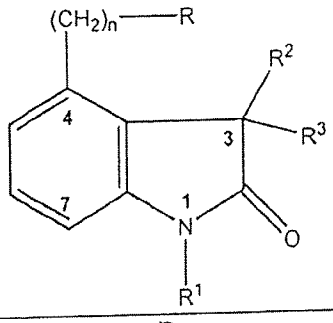
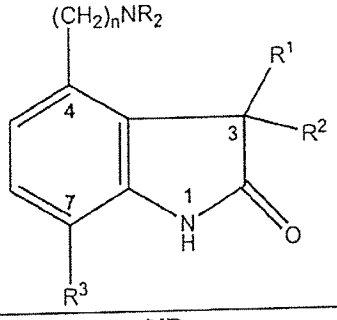
COMPARISON OF GENUS CLAIMS IN '944, '808, & '860 PATENTS

'944 Patent	'808 Patent	'860 Patent
		
R	**R**	**NR_2**
Amino	Amino	Amino (when both R's = H)
Lower alkylamino	C_{1-6} lower alkylamino	C_{1-4} alkylamino (when one R = H and the other R = C_{1-4}-lower alkyl)
di-loweralkylamino	di-(C_{1-6}-loweralkyl)amino	di-(C_{1-4}-loweralkyl)amino (when both R's = C_{1-4}-lower alkyl)
	allylamino	
di-N-allylamino	diallylamino	
N-allyl-N-lower alkylamino	N-(C_{1-6}-lower alkyl)-N-allylamino	
	benzylamino, dibenzylamino	
	phenethylamino, diphenethylamino	
	4-hydroxyphenethyl amino, di-(4-hydroxyphenethyl)amino	
R^1	**(position not designated)**	**R^3**
Hydroxy (OH)		Hydroxy
Methoxy (OCH_3)		
	Hydrogen	Hydrogen
(position not designated)	**R^1**	**(position not designated)**
Hydrogen	Hydrogen	Hydrogen
	C_{1-4}-lower alkyl	
(position not designated)	**R^2,R^3 (independently)**	**R^1,R^2 (independently)**
Hydrogen	Hydrogen	Hydrogen
	C_{1-4}-lower alkyl	C_{1-4}-lower alkyl
n	**n**	**n**
1-3	1-3	1-3

The fact that GSK drafted narrow genus claims appropriate for each patent reflects a conservative, careful, and considered approach to prosecuting this family of patents.

235. As with the '808 patent, the prosecution of the genus claim in the '860 patent proceeded in a manner consistent with standard practice in the pharmaceutical industry then and today. REDACTED The claim sought by GSK is reasonable.

236. The patent examiner who examined the '860 patent had before him the genus disclosed in the '944 patent and the '808 patent. Given the disclosure, it would have been reasonable to conclude that the claimed genus of the '860 patent would possess the asserted utility.

237. Dr. Owen did not fail to disclose any material information with respect to the invention of the genus claims of the '860 patent.

238. There is no evidence of an intent to deceive the Patent Office concerning inventorship of the generic claims of the '860 patent.

2. ***Allegations Regarding Bromocriptine***

239. In the background section of the patent, prior art ergot alkaloid compounds to treat Parkinson's disease are described and criticized for their side effects. PTX 35, col. 1, lines 36-44. One of these compounds is bromocriptine, which is described as a "post-synaptic" dopamine agonist.

240. The description of bromocriptine as "post-synaptic" is correct.

241. The compounds of the '860 patent are indolones having a fundamentally different

structure than ergot alkaloids. The basis of patentability was that these indolones had a central nervous system effect contrary to what was previously thought. *Id.*, col. 1, lines 48-58. The description of the ergot alkaloids and their side effects in the patent is solely as a predicate for the conclusion that there was a continuing need for effective treatments of Parkinsons Disease. *Id.*, col. 1, lines 35-48.

242. Nothing in the patent or its prosecution supports the proposition that whether bromocriptine was or was not "post-synaptic" would have been material to the prosecution of the '860 patent. During prosecution of the European counterpart to the '860 patent, the alleged error was drawn to GSK's attention and the description of bromocriptine was (perhaps incorrectly) changed. Regardless, the European patent was issued without incident.

243. The statement regarding bromocriptine was not material.

244. Dr. Owen did not make any false statements with respect to bromocriptine.

245. There is no evidence of an intent to deceive the patent office with respect to bromocriptine.

3. *Allegations Regarding False Inventorship*

246. For the reasons indicated above, Dr. Owen, not Professor Costall or any other Bradford researcher, is properly designated as the sole inventor of the '860 patent.

II. PROPOSED CONCLUSIONS OF LAW

A. Validity

247. A duly issued patent is presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims. 35 U.S.C. § 282.

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248. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity. 35 U.S.C. § 282. One seeking to prove a patent is invalid must do so by clear and convincing evidence. *See, e.g., Kahn v. General Motors Corp.*, 135 F.3d 1472, 1480 (Fed. Cir. 1998).

B. Anticipation

249. A patent is anticipated under 35 U.S.C. § 102(b) if "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States . . ." 35 U.S.C. § 102(b) (2000); *Minnesota Min. & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed. Cir. 2002).

250. For prior art to anticipate under 35 U.S.C. § 102(a) because it is "known," the knowledge must be publicly accessible, and it must be sufficient to enable one with ordinary skill in the art to practice the invention. *Minnesota Min. & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed. Cir. 2002).

251. A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. *Lewmar Marine, Inc. v. Barient Inc.*, 827 F.2d 744, 747 (Fed.Cir.1987). Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed.Cir.2003).

252. Teva has failed to carry its burden of demonstrating that the claims in the '808 patent are anticipated.

253. Teva has failed to carry its burden of demonstrating that the claims in the '860 patent are anticipated.

C. Obviousness

254. A patent is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. 35 U.S.C. § 103(a); *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 2006 WL 2806466 at *4 (Fed. Cir. 2006).

255. The standard obviousness inquiry requires specific factual findings on: (1) the scope and content of the prior art; (2) the level of ordinary skill in the field of invention; (3) differences between the claimed invention and the prior art; and (4) objective indicia of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Yamanouchi Pharm. Co. v. Danbury Pharmcal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000).

256. In the context of chemical compounds, a prima facie case of obviousness may be proven by showing a "[s]tructural similarity between the claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions." *Yamanouchi Pharm.*, 231 F.3d at 1343. The prior art must also offer a "reasonable expectation of success," although not "absolute predictability." *Id.*

257. A *prima facie* case of obviousness can be rebutted by showing "'unexpected results,' *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

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258. If all claim limitations are found in a number of prior art references, the fact finder must determine "[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references." *Dystar* at *4; *In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004).

259. The use of hindsight is inappropriate in determining whether an invention is obvious; rather, courts must be careful to "guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention at issue." *Graham*, 383 U.S. at 36; *Dystar* at *4.

260. Obviousness requires one of ordinary skill in the art to have a reasonable expectation of success as to the invention. "[O]bvious to try" and "absolute predictability" are incorrect standards. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). The presence of a reasonable expectation of success is measured from the perspective of a person of ordinary skill in the art at the time the invention was made. *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000).

261. Objective indicia, or "secondary considerations" of non-obviousness include "commercial success, unexpected results, copying, long-felt but unresolved need, and the failure of others to develop the invention." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005) (citing *Graham*, 383 U.S. at 17-18).

262. Teva has failed to carry its burden of demonstrating that the claims in the '808 patent are obvious.

263. Teva has failed to carry its burden of demonstrating that the claims in the '860 patent are obvious.

264. Even without application of the Federal Circuit's "teaching-suggestion-motivation" test, Teva has failed to carry its burden. *See generally, Dystar*, 464 F.3d 1356.

D. Inventorship

265. "Conception is the touchstone to determining inventorship." *Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997) (citing *Sewall v. Walters*, 21 F.3d 411, 415 (Fed. Cir. 1994)). "Conception is the 'formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice.'" *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986) (quoting 1 Robinson on Patents 532 (1890)). "An idea is sufficiently 'definite and permanent' when 'only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation.'" *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1998) (quoting *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994)).

266. The named inventors on an issued patent are presumed to be the true and only inventors. *Hess v. Advanced Cardiovascular Sys., Inc.*, 106 F.3d 976, 980 (Fed. Cir. 1997), *cert. denied*, 520 U.S. 1277, 117 S.Ct. 2459 (1997). "Any party wishing to challenge the . . . patent's current inventorship must ultimately come forward with clear and convincing evidence of facts that support its contentions." *Fina Oil & Chemical Co. v. Ewen*, 123 F.3d 1466, 1472 (Fed. Cir. 1997) (citing *Hess*, 106 F.3d at 979-80). Corroborating evidence, preferably a contemporaneous disclosure, is required for proof of conception. *See, e.g., Burroughs Wellcome*, 40 F.3d at 1228.

267. "[A] joint inventor must contribute in some significant manner to the conception of the invention. As such, 'each inventor must contribute to the joint arrival at a definite and

permanent idea of the invention as it will be used in practice.'" *Fina* (citations omitted) (quoting *Burroughs Wellcome*, 40 F.3d at 1229).

268. Furthermore, the Federal Circuit has held that a person does not become a co-inventor by: (1) "merely assisting the actual inventor after conception of the claimed invention;" (2) "simply provid[ing] the inventor with well-known principles or explain[ing] the state of the art without ever having a 'firm and definite idea' of the claimed [invention] as a whole"; or (3) "simply reduc[ing] the inventor's idea to practice." *Ethicon*, 135 F.3d, at 1460 (citations omitted).

269. Teva has failed to carry its burden of demonstrating any errors or misconduct in the naming of Gregory Gallagher as the sole inventor of the inventions claimed in the '808 patent.

270. Teva has failed to carry its burden of demonstrating any errors or misconduct in the naming of David Owen as the sole inventor of the inventions claimed in the '860 patent.

E. Inequitable Conduct

271. Applicants for patents have a duty to prosecute patents in the United States Patent and Trademark Office ("USPTO") with candor and good faith, including a duty to disclose information known to the applicants to be material to patentability. A breach of this duty may constitute inequitable conduct, which can arise from an affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive or mislead the USPTO.

272. A party asserting that a patent is unenforceable due to inequitable conduct must prove materiality and intent by clear and convincing evidence. Once threshold findings of materiality and intent are established, the trial court must weigh them in order to determine

whether the equities warrant a conclusion that inequitable conduct occurred. This inquiry requires a careful balancing: when the misrepresentation or withheld information is highly material, a lesser quantum of proof is needed to establish the requisite intent. In contrast, the less material the information, the greater the proof must be. *Purdue Pharma L.P. v. Endo Pharm., Inc.*, 438 F.3d 1123, 1128-29 (Fed. Cir. 2006) (citations omitted).

273. Information is material "when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

37 C.F.R. § 1.56(b). *Purdue Pharma*, 438 F.3d at 1129. Information is deemed material if there is a substantial likelihood that 'a reasonable examiner would have considered such prior art important in deciding whether to allow the parent application.'" *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1363 (Fed. Cir. 2003) (quoting *Driscoll v. Cebalo*, 731 F.2d 878, 884 (Fed. Cir. 1984)).

274. Teva has failed to carry its burden of demonstrating that GSK made material misstatements to the USPTO in securing the '808 patent.

275. Teva has failed to carry its burden of demonstrating that any alleged misstatements by GSK in securing the '808 patent were made with intent to deceive.

276. Teva has failed to carry its burden of demonstrating that GSK withheld any

material information from the USPTO in securing the '808 patent.

277. Teva has failed to carry its burden of demonstrating that any material information allegedly withheld by GSK in securing the '808 patent was withheld with an intent to deceive.

278. Teva has failed to carry its burden of demonstrating that the genus claim in the '808 patent was unreasonable.

279. Teva has failed to carry its burden of demonstrating that GSK committed inequitable conduct in securing the '808 patent.

280. Teva has failed to carry its burden of demonstrating that GSK made material misstatements to the PTO in securing the '860 patent.

281. Teva has failed to carry its burden of demonstrating that any alleged misstatements by GSK in securing the '860 patent were made with intent to deceive.

282. Teva has failed to carry its burden of demonstrating that the genus claim in the '860 patent was unreasonable.

283. Teva has failed to carry its burden of demonstrating that GSK committed inequitable conduct in securing the '860 patent.

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ATTACHMENT A

EXHIBIT 20 TO PROPOSED PRETRIAL ORDER

GSK's Proposed Findings of Fact
Glossary of Terms

Term	Definition
acute and repeat dosing studies	Preclinical testing that is performed in animals where the effect of a drug at various doses and at varying periods of time is measured.
adenylate cyclase test	A test for dopamine-sensitive adenylate cyclase.
adjunctive treatment	A drug used in combination with one or more other drugs for treatment.
agonist	A compound that is recognized by a receptor in the same way as its natural neurotransmitter and has the same effect on the target cell.
alkyl groups	Carbon atoms that are linked in a chain with the corresponding number of hydrogen atoms attached.
amino group	A common functional group that is denoted NH_2. It can also be an amine.
antagonist	A drug that interacts with the receptor in a way that is different from the natural neurotransmitter that results in the receptor being blocked from accepting natural neurotransmitter.
anxiolytic	A term for anti-anxiety.
aromatic	A chemical state where the bonds of a ring system lose their individual identity to form an extremely stable ring system, e.g. benzene, pyrole etc.
basal ganglia	An area of the brain that is involved with body movement.
blood-brain barrier	A physical barrier between the vascular system and the brain, which limits the types of substances that can pass from the blood into the brain.
bradykinesia	A state of slowness of movement.
catechol	A benzene ring with two adjacent hydroxyl groups substituted on it.
catechol mimetic	A compound or portion of a compound that mimics the chemical and biological activity of a catechol.
catecholamine	A name for all organic compounds that have both a catechol nucleus and an amine group.
caudate-putamen	The common name for the striatum in Man.

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central nervous system (CNS)	The collection of neurochemical pathways within the brain and spinal cord.
clinical trials	Experiments performed with pharmaceutical compounds in humans after initial regulatory approval has been obtained.
confinement motor activity test	An *in vivo* test for central behavioral effects of a compound.
conformations	Molecules with the same chemical composition and structure, but with different three-dimensional forms.
conscious animal studies	Preclinical experiments performed on conscious animals.
dopamine agonist	A compound that binds with a dopamine receptor and inducing the same pharmacological response as dopamine.
dynamic range	The dose range across which a drug can be used.
dyskinesia	A medical term for involuntary movements.
emesis	A medical term for vomiting.
ergoline-type dopamine agonists	Compounds that are based on the ergot alkaloids that have the same pharmacological response as dopamine.
ergot alkaloids	Alkaloids that are isolated from the dried sclerotium of the fungus *Claviceps purpurea*.
functional groups	Common molecular fragments that have characteristic chemical properties.
GABA receptors	Receptors that are activated by GABA, a common inhibitory neurotransmitter.
generic claim	A patent claim that covers more than a single chemical compound.
genus claim	A patent claim that covers more than a single chemical compound.
hepatic drug metabolism	Metabolism that occurs in the liver.
heterocyclic rings	A ring system in a chemical structure that has non-carbon as a component of the ring.
hexobarbital test	A test that is used to asses the sedative character of a compound.
hydroxyl group	A common functional group that is denoted -OH or HO-. It may also be called a hydroxy group.
hydroxylation	The process of adding a hydroxyl group to a compound.
in vitro test	A test not performed on a live animal or human.

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in vivo test	A test performed on a live animal or human.
indole	Defined as a bicyclic ring system composed of a benzene ring attached to a heterocyclic 5-membered ring containing a nitrogen atom. Between the 2' and 3' positions of the ring there is a carbon-carbon double bond. Both rings are aromatic.
indolone	A bicyclic ring system composed of a benzene ring attached to a heterocyclic 5-membered ring containing a nitrogen atom. At a point on the 5-membered ring a ketone group (=O) is substituted for two hydrogen atoms.
isomers	Molecules with the same chemical composition, but with different structures.
ketone group	A common functional group composed of carbon double bonded to oxygen and is denoted C=O. It may also be called a carbonyl group
lead compound	A molecule that shows some of the desired biological activity.
lipophilicity	The attraction of a compound to certain organic compounds such as fats.
locomotor	Progressive movement or the act of moving from place to place.
medicinal chemistry	The science of designing and developing new compounds for therapeutic use.
metabolic activation	The situation that occurs when a compound is either mildly active or inactive when administered, but through metabolic pathways in the body the compound is altered and becomes biologically active.
metabolize	The process by which an organism uses and eliminates a substance from the body.
molecular framework	The carbon backbone or ring system of a molecule.
molecules	Groups of atoms connected together to form a larger structure.
monotherapy	A stand-alone drug treatment.
neurodegenerative disease	A disease in which a subset of nervous system cells lose function and die.

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MPTP-Treated Marmoset Model	An animal model that determines the level of anti-parkinsonian activity that a compound has by treating an animal that has been given MPTP which mimics the symptoms of Parkinson's Disease
neurotransmitter	Compounds that are critical to the transmission of signals between neurons.
norepinephrine	A neurotransmitter that, when released from its nerve cells, raises the blood pressure among other actions.
organic chemistry	The scientific study of the structure, properties, composition, reactions, and preparation (by synthesis or by other means) of chemical compounds of carbon and hydrogen, which may contain any number of other elements.
organic compound	Molecules typically composed of carbon (C), hydrogen (H), nitrogen (N), and oxygen (O) atoms, sometimes with additional elements.
Parkinson's Disease	A degenerative disease of the central nervous system that affects the control of muscles.
perfused rabbit ear artery test	A test for peripheral D2 agonist activity.
Peripheral nervous system	The collection of neurochemical pathways outside of the brain and spinal cord.
pharmacology	The study of how drugs produce a change in function within an organism.
pharmacophore	The portion of the molecule responsible for its biological activity.
Porsolt test	A test used to measure the anti-depressant activity of a compound.
postsynaptic end	The beginning of a nerve cell after a synaptic cleft.
preclinical trials	Experiments performed with pharmaceutical compounds in animals.
presynaptic terminal	The end of a nerve cell before a synaptic cleft.
prodrug	A compound that on it own has little or no biological activity, but becomes biologically active after it is metablolized, either by adding or subtracting functional chemical groups to or from it.
receptor	The site of action of a particular neurotransmitter.

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Restless Legs Syndrome	A condition where the patient has the uncontrollable urge to move her legs, often accompanied by various uncomfortable sensations in the legs.
species	In the field of chemistry, a specific type of atomic nucleus, atom, ion, or molecule.
stereotypy	Abnormal physical movement characterized by sniffing or gnawing, often an indication of CNS drug effects.
striatum	The location in the brain where dopamine is released and acts on target cells that posses dopamine receptors.
Structure Activity Relationships (SAR)	A conceptual approach used by medicinal chemist to try and determine which structural portions of an active molecule result in the observed pharmacological response in order to be able to come up with new molecules that will produce the desired response.
substantia nigra	The portion of the basal ganglia where dopamine producing nerve cells originate.
substituents	The various functional groups that are placed on a molecular frame work.
synapse	The point of connection between two nerve cells or between a nerve cell and tissue.
synaptic cleft	The space between the end of one nerve cell and the beginning of another.
synaptic transmission	The process of the neurotransmitter passing across the synaptic cleft and binding to the receptor.
tachyphylaxis	A decreasing response to a drug (drug tolerance).
target	A point of focus for a pharmaceutical researcher on a specific biological mechanism of action that is thought to play a role in the disease.